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ORIGIN OF MOTOR REACTIONS PRODUCED BY ELECTRICAL STIMULATION OF THE CEREBRAL CORTEX

J. G. DUSSER DE BARENNE, M.D.

NEW HAVEN, CONN.

Since the discoveries of Hitzig (1870), knowledge of the functions of the cerebral cortex has been vastly increased. The methods of extirpation of various parts and areas of the cortex and of electrical and chemical stimulation have yielded and still yield valuable information. Notwithstanding this remarkable progress, insight is still lacking into many fundamental problems. One of the principal reasons for this obscurity is undoubtedly the stupendous complexity of the structure of the cortex, concerning which even modern histologic methods warrant only a vague surmise. I refer here especially to the complexity of the cortex in cross-section, in a direction perpendicular to the surface.

One finds here, more or less distinctly in various regions of the cortex, an arrangement of the myriads of nerve cell bodies in a few layers. A fundamental subdivision in six layers is nowadays generally accepted. This arrangement is suggestive of separation and difference in function; it has indeed often been stated that these layers represent, to some extent, separate functional units. On the other hand, one must always keep in mind the fact that the layers are most intricately interwoven. The processes of the constituent cells of every layer—with the exception of the first, most superficial one—ramify extensively into the other layers, often into as many as four or five of them; this indicates a high degree of integration, of close correlation and interaction. Obviously any subdivision of the cerebral cortex must be arbitrary and to some extent artificial.

Very little is known as yet about the functions of these various layers, and the little that is known (or assumed) is derived exclusively from histologic and anatomic studies. It is known that in the giganto-pyramidal area of the cortex (field 4 of Brodmann) the giant pyramidal cells of the fourth layer give rise to most of the nerve fibers descending along the brain stem into the spinal cord as fibers of the pyramidal

From the Laboratory of Neurophysiology, Yale University.

Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

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tracts. At present the view advocated by Ariëns Kappers and Bielschowsky is rather generally accepted, that the three or four outer layers are predominantly receptive in function and that the two inmost layers more particularly subserve efferent functions. Nissl, van Valkenburg and Nieuwenhuyse have also argued for a relative independence of and antagonism between the four outer and the two inner layers. A few additional, although indeed less probable, assumptions might perhaps be made; but this would be all. Physiology has not as yet spoken on this subject because until recently no experimental method of attack, of simplification in this bewildering complexity of the cortex, was known.

At present such a method is available, namely, *the method of laminar thermocoagulation,*[1] which permits one to destroy at will any number of consecutive layers of the cortex and to leave the other layers intact. Local application of moderate heat (of temperatures little above the coagulation temperatures of the living nerve tissue[2]) to the exposed cortex for very short periods results in destruction of the nerve tissue; by employing different temperatures and different periods of application, it is possible to "dose" the depth of the destruction and thus to produce laminar lesions. It has been found that warming the cortex to 65 C. for two seconds destroys the nerve cells of the two outer layers and that heating to 70 C. for three or four seconds leads to destruction of the three or four superficial layers, whereas application of a temperature of 80 C. for five seconds destroys all the nerve cells throughout the whole thickness of the cortex.

TECHNIC

The apparatus used in these experiments is simple. Inside a small coil wound on a porcelain tube (such as a resistor of from 20 to 30 watts and 1000 ohms, 5 cm. long) slides a small cylindric brass bar of suitable diameter. Into one of the ends of the bar small pieces of brass of various shapes (round or rectangular) can be screwed. The surfaces of some of these tips are made slightly concave to fit the convexity of the cortex of the higher mammals (cats, dogs and monkeys). A flat surface may be used for experiments on the brain of the rat or the rabbit. The dimensions used until now are: for the rectangular surfaces, 5 by 7 mm.; for the round surface, a diameter of 8 mm.; for the circular surface, a ring of 1 mm. width and of 7 mm. internal diameter. These surfaces may be heated to any temperature suitable for the purpose by connecting the leads of the heating resistor to a power outlet in series with a sliding rheostat (of, for instance, 1,200 ohms, 1 ampere). The temperatures on the surfaces of the tips are determined in the usual way with thermocouples and a ballistic galvanometer, and thus a series of settings of the rheostat is established for a few suitable temperatures (60, 70, 80, 90 and

1. Dusser de Barenne, J. G.: Science **77**:546, 1933; Ztschr. f. d. ges Neurol. u. Psychiat. **147**:280, 1933; Arch. f. d. ges. Physiol. **233**:529, 1933.

2. I have been unable to find statements about the coagulation temperatures of the proteins of the living cortex. I have had, therefore, to depend on the data in the literature on coagulation temperatures of various protein solutions.

100 C.) with each type of brass tip used. Over the other end of the brass bar a piece of rubber tubing is slipped, so that the rod is free to be moved upward and downward no more than 2 or 3 mm.

This heating device is so small that it may easily be handled when held with an ordinary hemostatic forceps; when used in sterile operations, only the brass heating tip need be sterilized.

The heating surface is brought into contact with the region of the cortex to be heated and presses against it by the weight of the brass rod; the apparatus, therefore, exerts a constant pressure against the cortex in every experiment, insuring reproducible lesions. If a larger area of the cortex is to be heated, for instance, the convexity of the whole precentral arm area, the thermode is applied repeatedly against the cortex in such a way that the successive heated areas are contiguous. In this way it is possible to obtain lesions of different size, penetrating to any desired depth into the cortex.

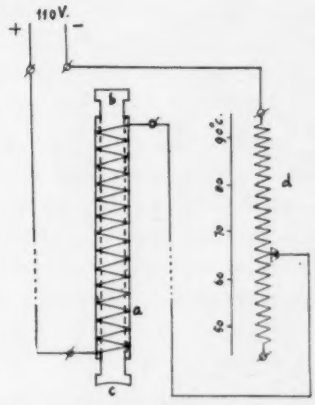

Fig. 1.—Diagram of the heating device used: *a*, heating resistor; *b*, cylindric brass bar, gliding in the interior of the porcelain tube of *a*; *c*, heating surface of *b*; *d*, sliding rheostat in series with *a* for adjustment of temperature of *c*.

The lesions made by this method are strictly delimited to the heated area, which under the microscope appears as an encapsulated area, sharply marked off from the surrounding cortex by a wall of proliferated connective tissue, neuroglia and blood vessels. If the operation has been accomplished under sterile conditions and if the animal has been kept surviving for four days or longer, all the nerve cells inside the heated area have disappeared. The cortex immediately outside the wall of proliferated tissue shows practically no alterations. The continuity of the surface of the cortex is unbroken, and the lesions are produced without any concomitant symptom of excitation. For further details the reader is referred to the description of the lesions given by Dr. H. M. Zimmerman (of the Department of Pathology of Yale University).[3]

This method of laminar thermocoagulation of the cerebral cortex results, therefore, within a wide range of temperatures in a sharply localized, selective destruction of the nerve elements. By selecting suit-

3. Dusser de Barenne, J. G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:280, 1933. The description referred to here extends from page 285 to 290.

able temperatures and suitable periods of application of the heat it is possible to destroy, at discretion, the nerve elements in any desired number of consecutive layers of the cortex.

The only limitation of the method is that it cannot be used, at least in its present form, for that part of the cortex which lies in the depth of the sulci.

This method, the first attempt at *laminar corticology,* allows an approach to many problems in the fields of physiology, anatomy and experimental pathology of the cerebral cortex.

OBSERVATIONS

One of the first problems attacked by this method is that of the origin of the motor reactions produced by electrical stimulation of the motor cortex, about which nothing is known as yet. In 1907, Lewandowsky [4] stated: "Whether the electrical stimulation spreads directly towards the giant pyramidal cells or whether it is conveyed by neural connections (which certainly exist) from the surface down to the deep layer of the giant pyramidal cells *cannot be decided*" [italics mine, D. de B.]). Von Monakow [5] was inclined to favor the latter view, although of course he could not bring any experimental support. The textbooks and handbooks of physiology and neurology published after 1914 that I have consulted do not even mention this problem.

A direct experimental approach to this problem is possible by destroying the three superficial layers of the motor cortex, e.g., in the arm region of a monkey, leaving intact the two inner layers.[6] The layer of the large and giant pyramidal cells would then be the first living layer of that part of the cortex. The first questions to be answered are: What are the motor reactions obtainable from such a cortex, and what is its excitability as compared with the reactions and excitability of that same cortex before the laminar thermocoagulation?

The following protocol may stand as representative of several experiments of this kind. As a matter of fact, this experiment yields such typical and such constant results that it can be used as a demonstration experiment.

MONKEY (Macacus rhesus) 9.

April 7, 1933.—2: 10 p. m.: Under ether anesthesia, sterile exposure was made of a large part of the convexity of the right hemisphere by elevating a flap of skin,

4. Lewandowsky, M.: Die Funktionen des zentralen Nervensystems, Jena, Gustav Fischer, 1907, p. 254.

5. von Monakow, C.: Gehirnpathologie, ed. 2, Vienna, A. Hölder, 1905; Die Lokalisation im Grosshirn und der Abbau der Funktion durch korticale Herde, Wiesbaden, J. F. Bergmann, 1914.

6. This motor cortex, especially field 4 of Brodmann, is characterized by the absence of the internal granular layer (layer 4) and therefore consists of only 5 layers.

bone and dura. Unipolar faradic stimulation was applied to various foci of the precentral arm area; the indifferent electrode was placed in the rectum. The threshold for the larger part of this area was found to be 12.5 cm.; from a focus in a small triangular area, bordering the face region, index finger and thumb movements were elicited with the threshold at 13.1 cm.

2:25 p. m.: Laminar thermocoagulation was applied to the convexity of the whole precentral arm area for three seconds at 70 C.

2:26 p. m.: No reactions were obtained from the arm area with the previously mentioned liminal strength of stimulation.

2:27 p. m.: Unipolar stimulation of the focus in the small triangle adjacent to the face region at 13.1 cm. coil distance resulted in distinct extension of the index finger and of the third and fourth fingers, with abduction of the thumb and slight extension of the wrist. This last movement appeared only after a few repetitions of the stimulation. Another sign of facilitation on repeated stimulation was the marked increase in the extent of the aforementioned finger movements.

2:40 p. m.: The wound was closed, as usual, in three layers; the dural flap was carefully closed.

3:55 p. m.: The operation was finished.

April 8.—9:00 a. m.: The animal was in excellent condition, alert and aggressive. There were no obvious disturbances in the left arm and hand. The monkey picked up food with this hand; it held a banana in the left hand while peeling it with the mouth and the right hand.

April 14.—The wound healed per primam.

10:05 a. m.: Under ether anesthesia, the right hemisphere was reexposed. The dura was not adherent to the cortex. The triangular lower part of the arm area, mentioned in the protocol of April 7, looked distinctly paler than the rest of the arm area. There was no marked difference between this cortex and the adjacent leg region. On unipolar stimulation of the focus in the middle of the triangular area a slight flexion of the contralateral thumb was obtained at 11.5 cm. coil distance. At 11.0 cm., there were discrete flexion of the thumb and abduction of the index finger. At 10.5 cm. there were the same movements, though stronger and with slight, but definite, facilitation on repetition of the stimulation.

10:51 a. m.: At 10.5 cm. coil distance, the first movement from the central focus of the triangular area was abduction of the thumb. The second stimulation resulted in adduction of the thumb, extension of the fingers, and extension of the wrist and flexion of the elbow. Monopolar stimulation at 11.0 cm. gave abduction of the thumb, and after facilitation (third stimulation) slight extension of the index and third fingers, but no response in the wrist and elbow. No reactions were obtained if the electrode was placed 0.5 mm. more frontally or occipitally from this specific focus.

The threshold for the other parts of the thermocoagulated convexity of the arm area was at 9.5 cm. The only movements obtained from this area were retraction of the shoulder and flexion of the elbow. The yield in fine, discrete movements from this larger area was certainly less than that obtained immediately after the thermocoagulation.

The animal was killed by deepening the anesthesia and stabbing the heart. The brain was placed in 96 per cent alcohol for histologic examination by Dr. H. M. Zimmerman, who was present during the part of the experiment performed on April 14.

Dr. Zimmerman has made Nissl preparations of the arm area and has studied the triangular region with its central focus in serial sections.

COMMENT

Figure 2 gives the general aspect of the cortex one week after the thermocoagulation and shows that the object of the experiment, namely, the destruction of the three superficial layers, has been attained. All the nerve cells in these layers have disappeared. The arrow marks the focus of stimulation, as it has been identified by Dr. Zimmerman by means of serial sections. In the fourth layer, immediately underneath the arrow, a single row of large pyramidal cells, among which is one

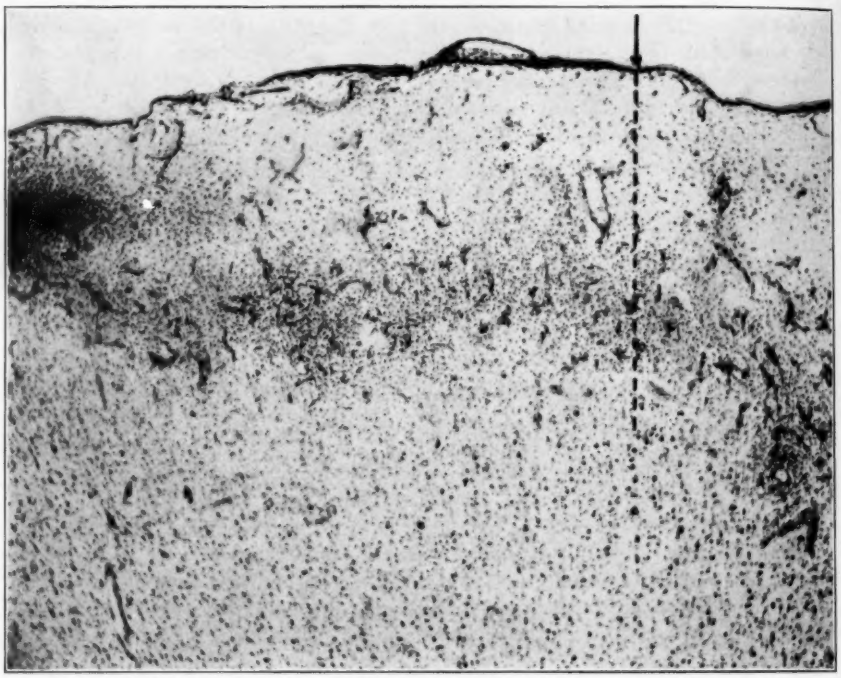

Fig. 2.—Part of the cortex of a monkey (Macacus) in which the three superficial layers of the whole precentral arm area, i. e., of the arm area of fields 4 and 6 of Brodmann, were destroyed by laminar thermocoagulation. The animal was killed seven days after operation. The arrow indicates the location of the focus of unipolar stimulation. The broken line through the cortex points toward a row of large pyramidal cells in the fourth layer. All nerve cells in the three outer layers have disappeared. Nissl preparation; magnification, × 42.

giant Betz cell, can be seen. No large pyramidal cells are found in the immediate neighborhood of this row of cells.

Figure 3 gives this column at a greater magnification (355) and shows distinctly that the cells have a normal appearance in the Nissl picture. From this experiment it follows: (1) that typical, apparently normal reactions can be obtained from the motor cortex when all the

nerve cells of the three superficial layers are killed; (2) that almost immediately after this thermocoagulation the threshold for these motor reactions is exactly the same as in the normal cortex prior to the laminar destruction. These two experimental facts prove definitively that these apparently normal motor reactions are obtained through the direct electrical stimulation of the nerve cells in the two inner layers of the motor cortex. The fact that histologic examination shows the presence of a

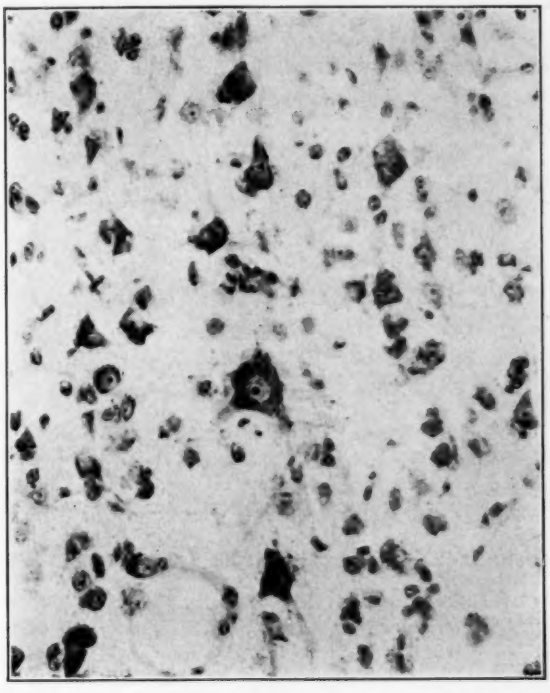

Fig. 3.—Part of the section shown in figure 2 at higher magnification (× 355) to show the column of large pyramidal cells, among which is one giant cell. This figure shows the normal appearance of these cells in a Nissl picture.

single column of large pyramidal cells (with one giant pyramidal cell) immediately underneath a selective focus, from the immediate neighborhood of which no reactions could be elicited, speaks strongly in favor of the conclusion that these motor reactions are brought about by the direct stimulation of these special nerve elements. In this particular experiment the threshold for unipolar cortical excitation was found to be higher than immediately after the destruction of the three outer layers. In other experiments, however, this threshold was found entirely normal.

The question still remains whether, when the normal motor cortex is stimulated electrically, the nerve cells of the three superficial layers participate in the production of the motor reactions obtained. If the superficial layers do not participate in the production of the motor reactions on electrical stimulation of the motor cortex, one might expect to find a difference in threshold when using the unipolar and the bipolar faradic method, as the distribution of the electric field must be quite different in the two cases. In the case of unipolar stimulation there is immediately below the electrode on the cortex a dense field, traversing the cortex almost perpendicularly and reaching the large and giant pyramidal cells, which lie about 1 mm. below the surface of the cortex, as a compact

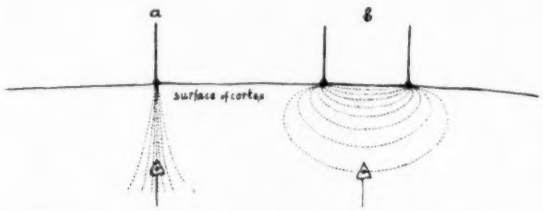

Fig. 4.—Diagram showing the distribution of stream-lines in the electrical field with unipolar (*a*) and bipolar (*b*) stimulation.

Threshold for Unipolar and for Bipolar Stimulation of the Brains of Three Monkeys

	Experiment 12			Experiment 13			Experiment 16		
Threshold, unipolar stimulation, cm. coil distance	12.4	12.5	11.3	12.2	13.0/15°	12.8	13.2	13.4	12.7
Threshold, bipolar stimulation, cm. coil distance	11.5	11.6	10.8	11.0	11.2	10.6	12.2	12.8	11.7

bundle or cone of stream-lines (fig. 4 *a*). With the method of bipolar stimulation, in which two electrodes are placed on the surface of the cortex 1 mm. apart (i. e., about as far apart as the average distance of the large pyramidal cells from the surface), the field must be entirely different (fig. 4 *b*). For the same difference of potential between the terminals of the secondary coil of the inductorium, the field is most likely less dense with the bipolar method than with the unipolar stimulation. Thus it might be expected that with the bipolar stimulation method a stronger stimulus will be needed to produce the same density of the electric field necessary to elicit direct excitation of the cell bodies of the deeper layers than with the unipolar method.

As a matter of fact, it was found that the threshold for unipolar stimulation is invariably distinctly lower than that for bipolar stimulation; in nine observations on various regions of the brains of three monkeys the average difference was 1.2 cm. (table).

The results of these observations point strongly toward the conception that the motor reactions evoked by electrical stimulation of the cortex are due to the direct stimulation of the cell bodies of the deeper layers of the cortex, and that neither the direct excitation of the dendritic processes of these cells ramifying in the upper cortical layers nor the excitation of the nerve cells of these superficial layers is essential in the elaboration of the stimulatory cortical reactions. At least no experimental evidence was met which favored the view that the superficial layers play a rôle.

From these observations, in conjunction with those in the earlier pages of this paper, the conclusion seems warranted that *the cortical reactions elicited by electrical stimulation of the excitable "motor" cortex are due to the direct excitation of the large and giant pyramidal cells of the fourth layer.*

SUMMARY

1. Apparently normal motor reactions can be obtained from the precentral electrically excitable cortex (area 4 of Brodmann) in monkeys after the thermocoagulation of its three superficial layers.

2. After a very short period of depression of excitability, lasting less than two minutes, the threshold for unipolar stimulation is found unchanged as compared with that obtained before the laminar thermocoagulation.

3. From the facts mentioned under 1 and 2 it can be concluded with certainty that apparently normal motor reactions can be elicited through electrical stimulation of a cortex in which only the nerve cells of the two inner layers are present.

4. Histologic evidence is given which strongly favors the conception that these reactions are due to the direct stimulation of the perikarya of the large and giant pyramidal cells of the fourth layer.

5. Experimental evidence is given which speaks in favor of the view that in stimulating the *normal* motor cortex the reactions obtained are also due to the direct electrical stimulation of the bodies of the nerve cells of the two deeper layers of the cortex.

6. No evidence was found pointing toward the participation of the three superficial layers. Thus all available evidence points toward the conclusion that the motor reactions obtained through electrical stimulation of the so-called motor cortex (area 4 of Brodmann) are elicited by the direct excitation of the bodies of the large and giant pyramidal cells of the fourth layer.

DISCUSSION

DR. W. PENFIELD, Montreal, Canada: This method opens up many avenues for study, pathologic as well as physiologic. Dr. Dusser de Barenne has shown a tremendous increase in the number of blood vessels in the area in question at the

end of one week. These vessels must have sprouted and grown in that length of time. Is there a greater increase at a later time, or is this the time of maximum increase?

Dr. J. G. Dusser de Barenne, New Haven, Conn.: I cannot answer Dr. Penfield's question. The point is at present under investigation. Furthermore, one of the first questions is: How do the nerve cells disappear? There is no trace of them within four days after the heating, so one must make a whole series of observations after one day or even less, two days, three days, four days and so on.

HISTOPATHOLOGY OF THE CENTRAL NERVOUS SYSTEM IN EPIDEMIC ENCEPHALITIS

(ST. LOUIS EPIDEMIC)

ARTHUR WEIL, M.D.
CHICAGO

The recent outbreak of epidemic encephalitis in St. Louis (summer, 1933) attracted considerable attention because it seemed different in many aspects from other epidemics. First, the seasonal incidence did not correspond with that of the great European epidemics which occurred at the end of, or shortly after, the World War. The report of the Matheson Commission [1] gave a detailed review of the different epidemics, indicating that most of the cases occurring between 1917 and 1927 were observed during the first quarter of the year, with a climax in February or March. The same is true of the epidemics of encephalitis in the United States during the years 1918 to 1928. The St. Louis epidemic, like the Japanese epidemics of 1924 and 1927, occurred during the summer, with a maximum in August and September. It should be noted, however, that, according to the *League of Nations Monthly Epidemiological Report* for September, 1927, "seasonable fluctuations are becoming more and more uncertain; there was thus a slight increase of the number of cases in June in several countries of northern Europe." The report for the years 1928 and 1929 supports this conclusion (p. 191).

Second, the clinical picture of the St. Louis epidemic seemed to differ from the classic description of the encephalitis lethargica which von Economo studied in Vienna in 1916 and 1917. In the latter cases the disease began with mild pharyngitis, followed by symptoms of meningitis, somnolence, oculomotor paralysis and delirium. Fever was not constant, and, if present, was of no definite type. About one half of the patients died. In the St. Louis cases, too, the disease began with mild pharyngitis and meningitis. Oculomotor paralysis, however, was absent throughout, and following the initial meningitis intense restlessness was a prominent symptom, which only later was followed by som-

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From the Institute of Neurology, Northwestern University.

Read before the Chicago Neurological Society, Dec. 21, 1933.

1. Matheson Commission: Epidemic Encephalitis; Etiology, Epidemiology, Treatment; Report of a Survey, New York, Columbia University Press, 1929, second report, 1932. (A complete survey of the literature is given in both volumes.)

nolence. In the cases ending in recovery, which was rapid and without prolonged reconvalescence in most instances, there were no "post-encephalitic" sequelae, such as chorea or parkinsonism, judging from reports published recently (December, 1933).

If one studies von Economo's [2] monograph, one finds that the later outbreaks of epidemic encephalitis in Vienna differed considerably from the epidemic of 1916 and 1917. Von Economo himself came to the conclusion that the clinical picture of epidemic (lethargic) encephalitis may show an immense variability in the combination of symptoms, which to the inexperienced seems unbelievable: ("diese ans Unwahrscheinliche grenzende Systemlosigkeit der Symptomenkombinationen." ["This lack of system in the combination of symptoms borders on the improbable"]). He differentiated between three main clinical groups: (1) the ophthalmoplegic-somnolent type, (2) the hyperkinetic type and (3) the amyostatic-akinetic type (parkinsonism). All three groups may be partially combined, or other types may be predominant: the cerebellar type, types characterized by acute bulbar paralysis, poliomyelitis, neuritis, vasomotor disturbances or disturbances of respiration, psychotic forms, abortive forms with diplopia and headaches only, etc. If one may judge from preliminary reports and from personal observations at the Isolation Hospital at St. Louis, most of the cases of this epidemic resembled the second, or hyperkinetic, type described by von Economo. As to the apparent absence of sequelae in many cases, one should refer to von Economo's observation that "nearly no cases with sequelae were observed during the first Vienna epidemic of 1916 and 1917, with the exception of two, which became chronic" (p. 206).

It seems, therefore, that neither the epidemiologist nor the clinician is in a position to decide whether the St. Louis epidemic is different from, or related to, the European epidemics or other American epidemics. In the following study the attempt will be made to decide whether it is possible to solve this problem with the help of histologic investigation.

With the assistance of the department of pathology of Washington University, St. Louis (Dr. Leo Loeb and Dr. H. A. McCordock), I was able to prepare histologic material from eight brains of patients with epidemic encephalitis, which forms the basis of this investigation.

RESULT OF PATHOLOGIC STUDIES

Gross Studies.—The formaldehyde-fixed material showed more or less marked congestion of the meningeal vessels, without any marked haziness or discoloration of the pia-arachnoid itself. There were exceptions in two cases (those of a woman, aged 67, and a man, aged 62), in which gross examination revealed haziness of

2. von Economo, C.: Die Encephalitis lethargica, Berlin, Urban & Schwarzenberg, 1929.

the pia-arachnoid, which, microscopically, was observed to be due to an increase in collagenic connective tissue fibers in connection with arteriosclerosis of the brain. On the cut surface of the white matter the engorged smaller vessels stood out as numerous red spots the size of pinpoints; no gross hemorrhages were observed, except in the corpus callosum in one case (that of a man, aged 61). Microscopic examination revealed that this was an organized area of hemorrhagic softening in connection with mild atherosclerosis of the larger cerebral vessels. In a second case (that of a woman, aged 63) small areas of hemorrhagic softening were present in the thalamus, together with a mild degree of calcification of the media of the smaller arteries. Microscopic examination in all the other cases showed no larger perivascular hemorrhages in areas of inflammatory reactions. Occasionally a few red blood cells were encountered outside a vessel with perivascular infiltration by round cells. But the well preserved outlines of the erythrocytes and the absence of scavenger cells pointed to a late, perhaps agonal, stage of these hemorrhages.

The configuration of the gyri was generally well preserved; no marked edema of the brain itself was noted.

Meningitis.—In each case leptomeningitis could be detected. Its intensity, however, varied in the different regions of the brain. The pia-arachnoid did not show

TABLE 1.—*Relative Intensity of Leptomeningitis in Different Regions*

Frontal Cortex	Central Cortex	Temporal Cortex	Midbrain	Pons	Cerebellum	Medulla Oblongata
0.8+	1.3+	1.2+	2.0+	1.2+	1.5+	0.7+

any inflammatory reaction over the frontal region in three cases or over the central region in two. The pia-arachnoid covering the temporal lobes, midbrain, cerebellum, pons and medulla oblongata was always more or less inflamed. The histologic picture varied from that of mild edema of the subarachnoid spaces, with scattered infiltration by round cells, to marked cellular infiltration of the pia-arachnoid (figs. 1 and 2). But even these pronounced inflammatory reactions were always confined to small, disseminated foci, with a preference for the sulci of the cerebral cortex and the cerebellum. Dense, diffuse infiltration, such as is seen in epidemic meningitis and, not infrequently, in the leptomeninges in acute anterior poliomyelitis, was never noticed. In most cases the cellular exudate consisted of lymphocytes, isolated plasma cells and histiocytes. Frequently, large scavenger cells filled with coarse granules which stained dark bluish green with cresyl violet were encountered. Polymorphonuclear leukocytes were absent, as were fragmentation of nuclei and other degenerative stages of the leukocytes. There was only a mild increase in fibroblasts, with new formation of collagenic fibers. In most of the cases with leptomeningitis a small number of red blood cells was intermingled with the cellular exudate. Shadow formation and the presence of iron-containing pigment outside and within scavenger cells indicated that these minute hemorrhages in the subarachnoid spaces must have occurred at an earlier period in the disease.

An attempt was made to determine the relative intensity of the leptomeningitis in the different cases. For this purpose the following gradation was adopted: + denoting isolated small round cells within the edematous pia-arachnoid; ++, mild cellular exudate in the adventitia of bloodvessels (veins and arteries alike),

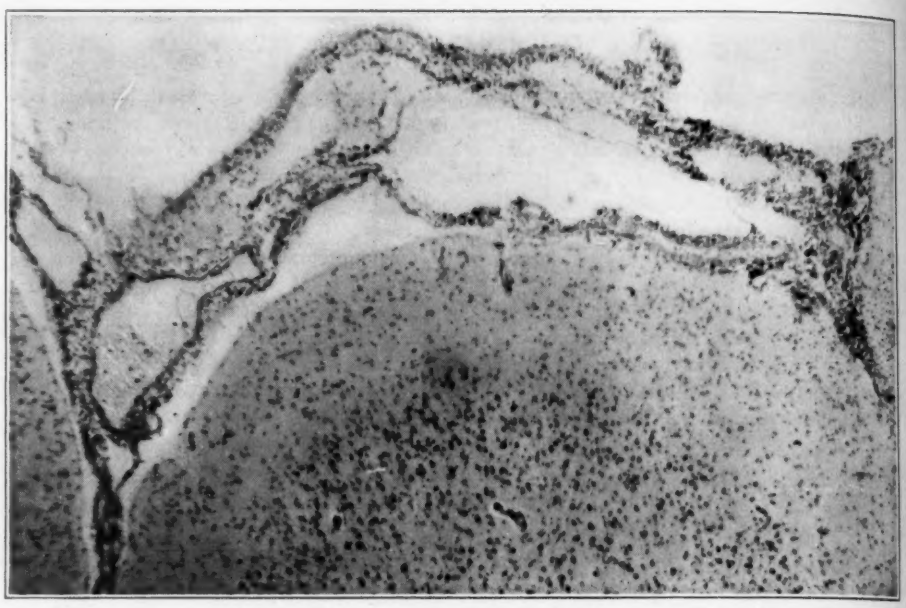

Fig. 1.—Section of the frontal lobe of a woman, aged 20, showing leptomeningitis. Cresyl violet stain; magnification × 50.

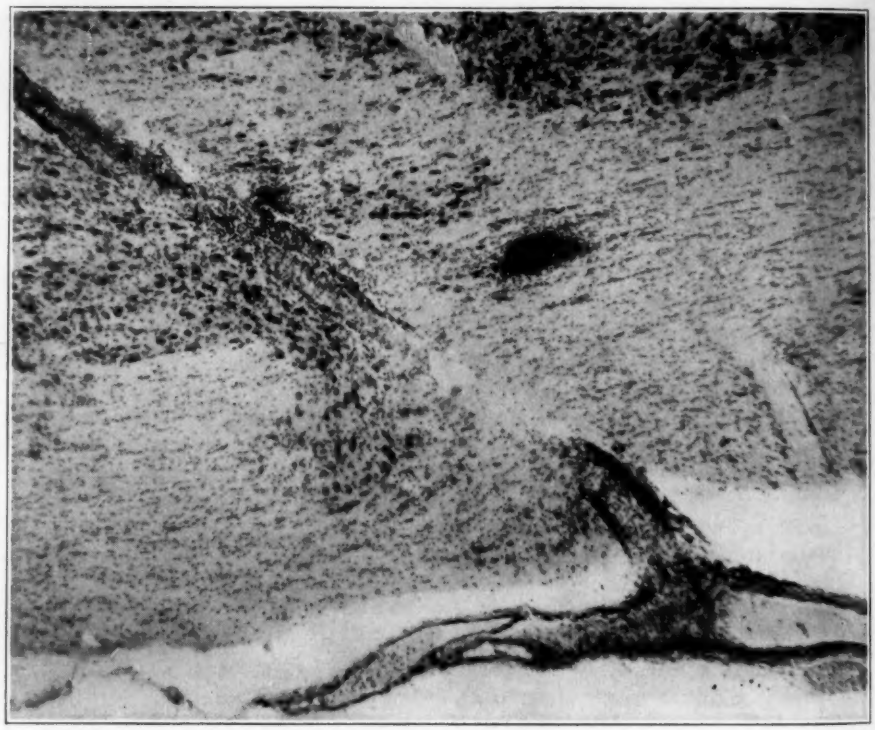

Fig. 2.—Same case as figure 1. Section of anterior surface of the pons, showing mild leptomeningitis, mild perivascular cellular infiltration and the formation of large foci of proliferated glia. Cresyl violet stain; magnification × 50.

and +++, dense perivascular cellular cuffing, with marked cellular infiltration of the subarachnoid spaces. All the plus marks were added, and the sum was divided by the number of slides and cases. The data obtained are shown in table 1.

Encephalitis.—The inflammatory reaction of the brain itself consisted of two different phases: perivascular infiltration by round cells and glial proliferation. The two processes were not always equal in intensity. In two cases the perivascular cellular exudation was much more pronounced than the glial proliferation, while in about one third of the cases the glial reaction was more predominant (fig. 3). In about one half of the cases the two were equal in intensity (figs. 4 and 5). It should

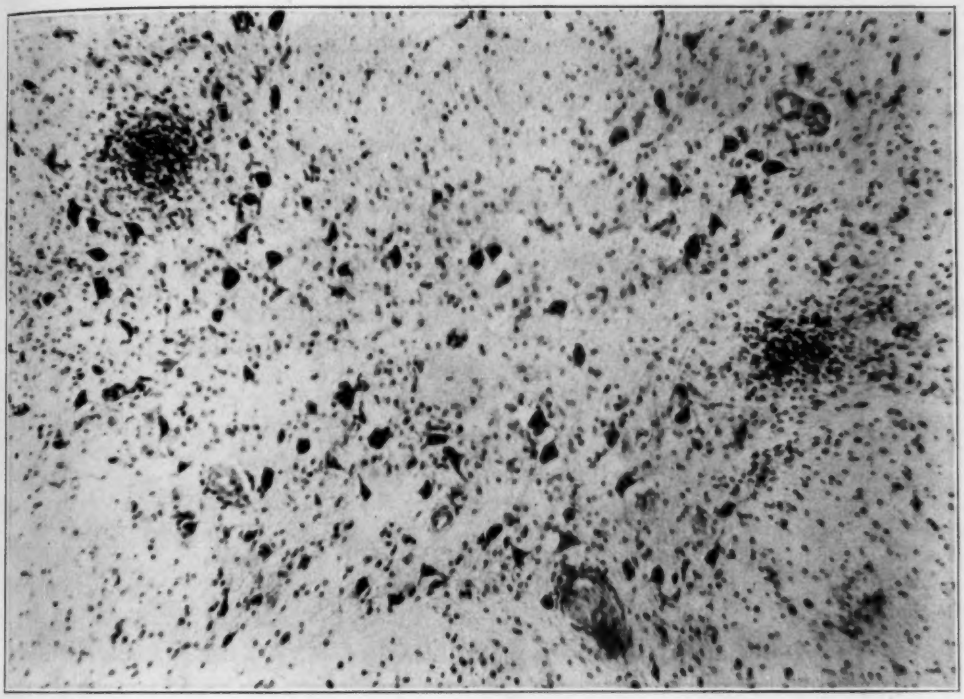

Fig. 3.—Section of the pons of a woman, aged 38, showing reticular formation, mild perivascular infiltration by round cells and foci of proliferated glia. Cresyl violet stain; magnification × 110.

be emphasized that the type of inflammatory response was the same throughout the brain in a given case, i. e., if the glial proliferation was more pronounced than perivascular cellular exudation in the striatum, the same type of inflammation could be found in the midbrain, pons and medulla oblongata of the same brain.

The perivascular cellular exudate resembled closely that described in the meninges. The main part was formed by small lymphocytes; occasionally, a polymorphonuclear leukocyte was seen; plasma cells were more numerous, but did not exceed 5 per cent of the perivascular round cells. Here, too, large scavenger cells loaded with dark bluish-green granular masses were occasionally seen.

The inflammatory reaction was observed around veins and smaller arteries alike. It was not confined to the cortical gray matter or the nuclear masses of the brain

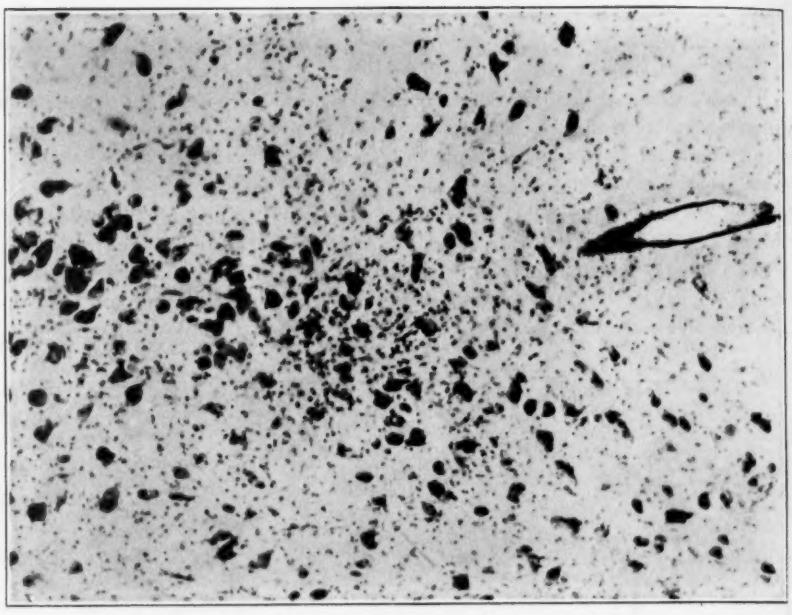

Fig. 4.—Section of the substantia nigra of a woman, aged 63, showing marked perivascular infiltration by round cells and glial proliferation. Cresyl violet stain; magnification × 100.

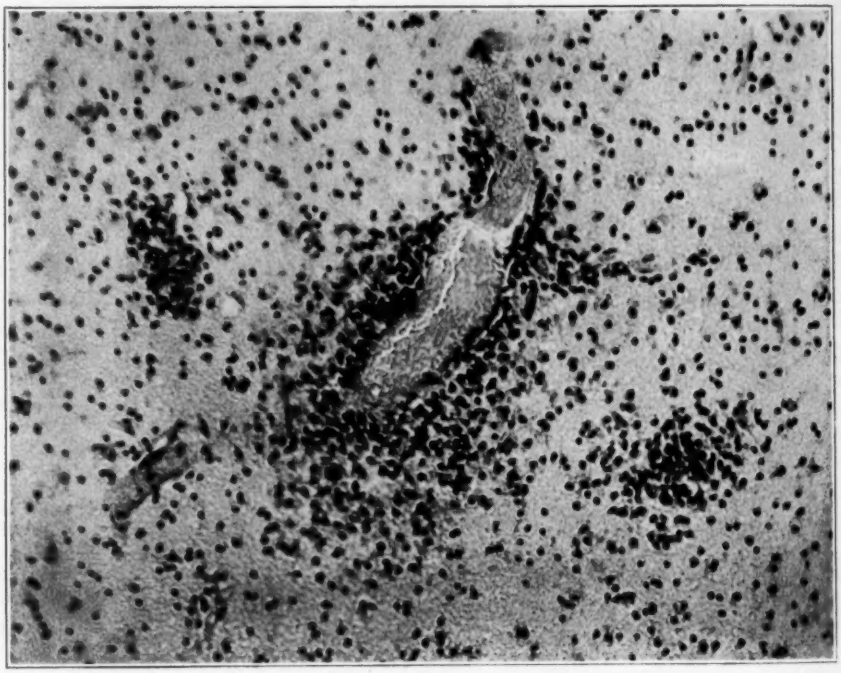

Fig. 5.—Section of the white matter of the central cortex of a man, aged 27, showing marked perivascular inflammatory reaction and glial proliferation. Cresyl violet stain; magnification × 170.

stem, but was seen in the white matter, in the subcortex and the cerebellar peduncles, being sometimes more pronounced than in the gray matter. Frequently, the accumulation of cells was more marked at one pole of a blood vessel cut longitudinally, but perivascular cuffing surrounding the whole circumference was seen just as frequently. The nuclei of the cells of the exudate were mostly well preserved, without marked fragmentation. In one case small abscess formations were present in the cerebellum and striatum around necrotic foci containing numerous colonies of small diplococci (figs. 6 and 7). Perivascular hemorrhages

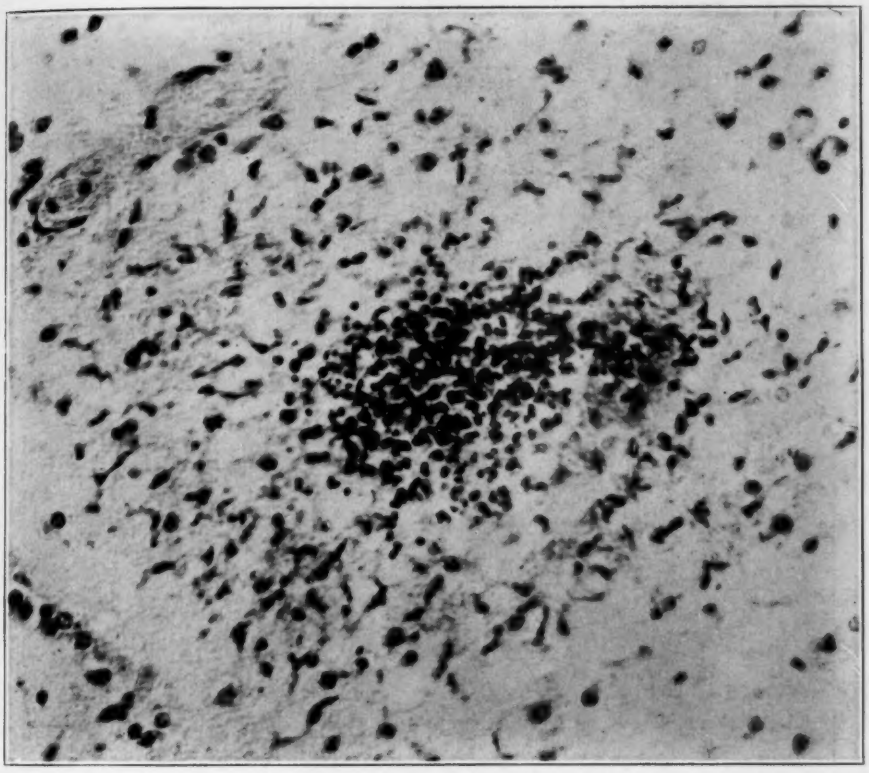

Fig. 6.—Section of the middle cerebellar peduncle of a man, aged 61, showing a focus of proliferated glia with fragmented nuclei surrounded by a wall of microglia. Cresyl violet stain; magnification × 300.

were absent, except in the two cases with arteriosclerosis already mentioned. Occasionally, isolated intact red blood cells were seen intermingled with the cellular exudate. In none of the cases was purpura of the brain (encephalitis hemorrhagica) observed, and necrosis of tissue did not belong to the histologic characteristics. The areas of anemic softening observed in two cases could easily be attributed to concomitant arteriosclerosis.

The foci of glial proliferation were as irregularly disseminated in the gray and white matter as the perivascular cellular exudate. They were independent of

blood vessels and were spread irregularly. Sometimes they were close to an area of perivascular cellular infiltration and in the immediate neighborhood of the zone of most intensive inflammatory reaction. In preparations stained with cresyl violet they consisted of nuclei of different shapes and sizes surrounded by a background that stained faintly purplish. Some of the nuclei assumed bizarre forms, resembling dumb-bells, clubs and the like; they were elongated or round. Others were shrunken or showed beginning fragmentation. By specific glial staining (Kanzler, Stern) it could be seen that the three different elements participated in the forma-

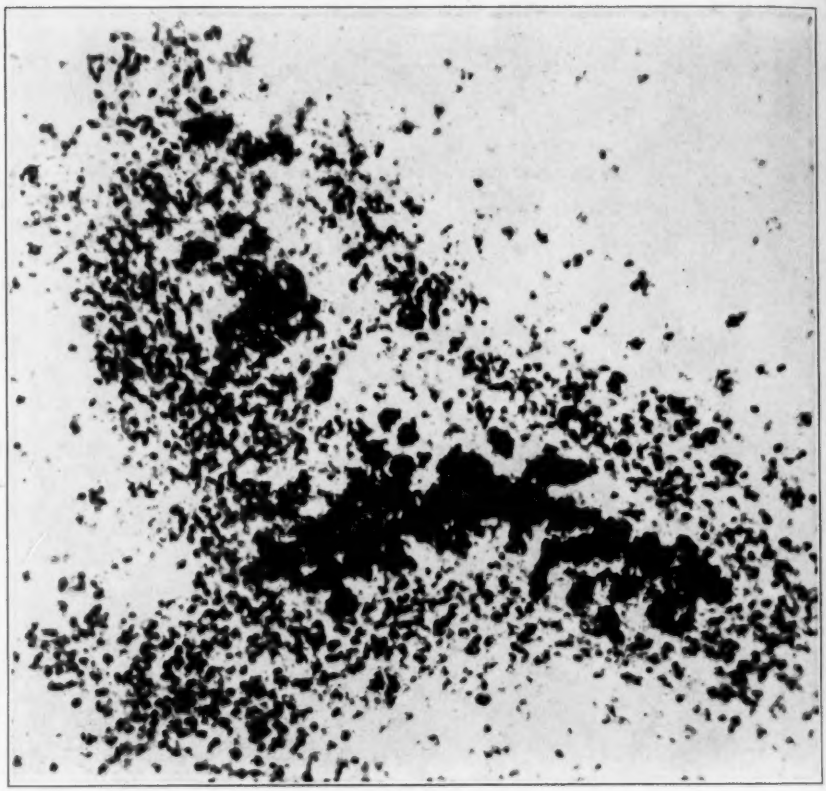

Fig. 7.—Same case as in figure 6. Section of the middle cerebellar peduncle, showing necrotic center of a focus of proliferated glia filled with numerous colonies of small cocci. Cresyl violet stain; magnification × 160.

tion of these foci; in most of them oligodendroglia were more predominant than microglia, astrocytes always being in the minority (fig. 8). In addition to pale-staining and well preserved forms, darker-staining and shrunken oligodendroglia and microglia cells were observed, which, judging from the form of the nuclei, belonged to the bizarre, dark-staining nuclei that were seen in preparations stained with cresyl violet (fig. 9). Compound granular corpuscles were not seen in the average case, except in the foci of anemic softening in the arteriosclerotic brains already described.

As with meningitis, an attempt was made to determine the relative intensity of perivascular infiltration by round cells and glial proliferation. For the former, standards were applied similar to those used in the classification of meningitis. For the glial proliferation the following gradation was adopted: + denoting small foci of a few glia cells in the neighborhood of a mild perivascular cellular exudation; ++, isolated small foci remote from blood vessels, and +++, many larger foci within the microscopic field (30 magnifications).

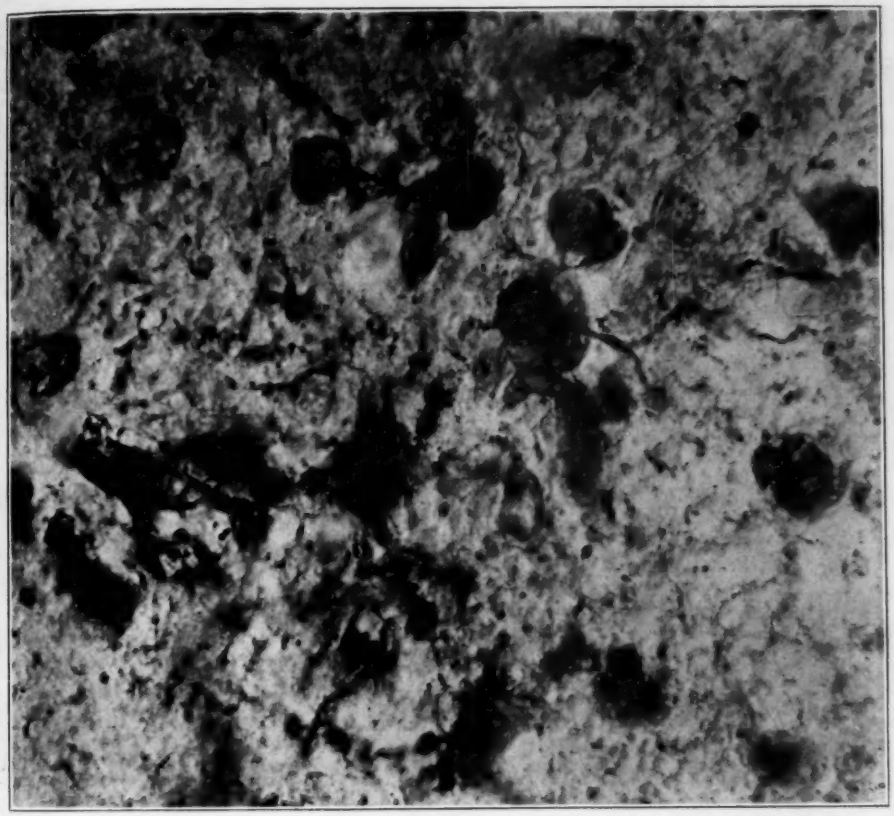

Fig. 8.—Same case as in figure 3. Section showing a small focus of proliferated glia, consisting mainly of oligodendroglia. Stern's method (Weil-Davenport modification); magnification × 1,100.

TABLE 2.—*Relative Intensity of Encephalitis in Different Regions*

	Frontal Cortex	Central Cortex	Temporal Cortex	Striatum	Thalamus	Midbrain	Cerebellum	Pons	Medulla Oblongata
Perivascular infiltration by round cells.....	1.1+	1.2+	1.0+	1.5+	2.0+	2.3+	1.3+	1.6+	1.8+
Glial proliferation.....	1.3+	1.6+	1.6+	1.4+	2.0+	2.5+	1.2+	2.2+	1.8+

Myelitis.—The inflammatory reaction, which was studied in the spinal cord in two cases, was essentially the same as that described for the brain. It was not confined to the gray matter, but occurred in the white matter also. Its intensity paralleled that of the encephalitis. It should be emphasized that in one case, in which the glial proliferation within the brain was much more pronounced than the perivascular cellular infiltration, the same relative intensity of both reactions was also seen in the spinal cord.

Ganglion Cell Disease.—Generalized disease of the ganglion cells was not seen in any of the cases studied. The disease was always localized in the immediate

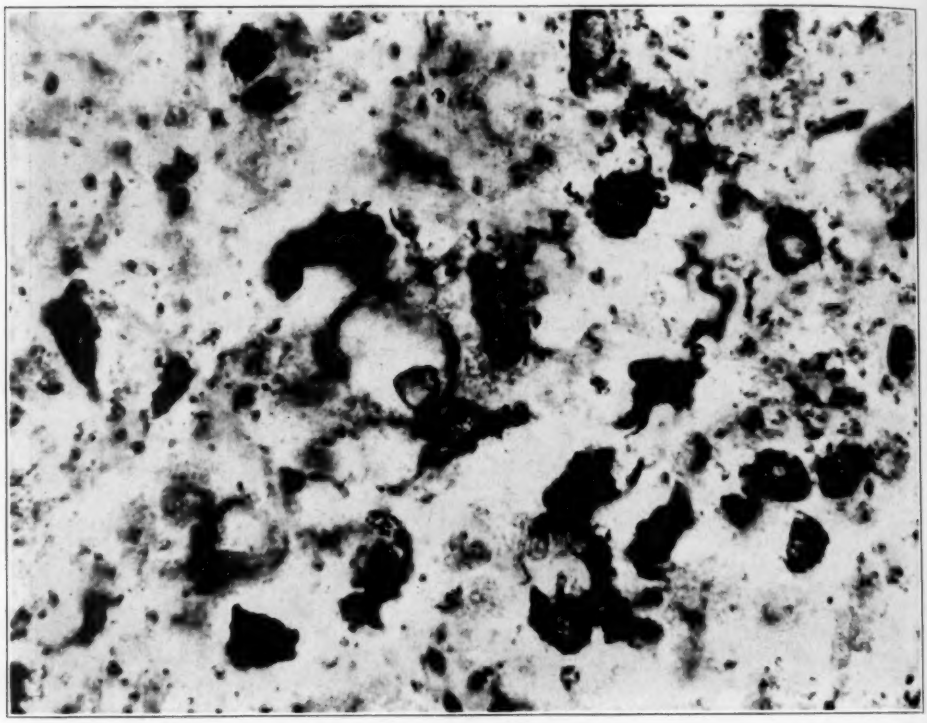

Fig. 9.—Same case as in figure 4. Section showing a focus of proliferated glia, with many shrunken and dark-staining cells. Stern's method; magnification × 1,600.

environment of foci of the inflammatory reaction. The best examples were observed in the substantia nigra and the anterior horn cells of the cervical spinal cord. The neurons next to infiltrated vessels or next to or within the foci of glial proliferation were severely diseased. Their cytoplasm was pale and showed either central chromatolysis or complete absence of Nissl's granules. The outlines were indistinct and sometimes shadow-like. The nuclei of these cells were swollen, the nuclear membrane being folded or pyknotic. Even in close proximity of these foci, the neurons showed only mild degrees of swelling and chromatolysis; they seemed fairly intact in regions remote from the foci (fig. 10). In cases in which arteriosclerosis of the brain was combined with the encephalitis, the cellular

changes, especially in the cortical gray matter, could well be ascribed to the arteriosclerosis. Isolated neuronophagia of neurons was rather uncommon; if the diseased ganglion cell was not buried in a focus of proliferated glia, only a mild increase in satellites was visible.

Myelin sheaths and axis-cylinders were not markedly involved. Even in the immediate neighborhood of the inflammatory foci the myelin sheaths showed only mild swelling, and areas of demyelinization were never seen around blood vessels or within the white matter.

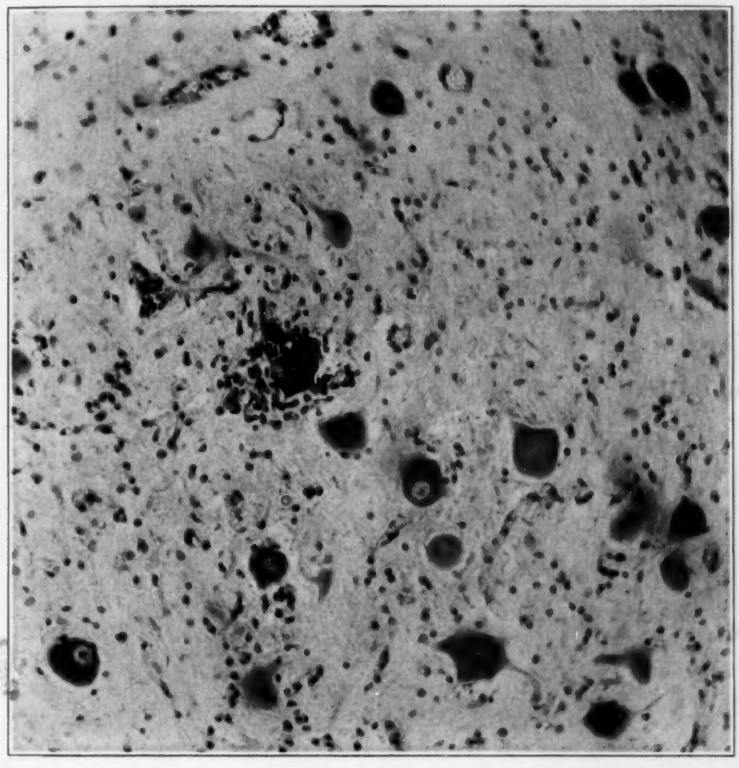

Fig. 10.—Same case as in figure 3. Section of the anterior horn of the cervical spinal cord, showing mild perivascular infiltration by round cells and glial proliferation around a diseased ganglion cell. The neurons in the immediate neighborhood of this focus show mild swelling or central chromatolysis. Cresyl violet stain; magnification × 85.

Demonstration of Micro-Organisms.—Micro-organisms were demonstrated in all the brains examined, as has been reported previously.[3] In all cases cocci were observed, frequently in the form of diplococci or short chains, in paraffin sections stained with cresyl violet. At first they were seen only occasionally, but with

3. Weil, A.: Demonstration of Micro-Organisms in Epidemic Encephalitis (St. Louis Epidemic), Arch. Path. **17**:278 (Feb.) 1934.

increasing experience the discovery was made easier by looking for pink, edematous areas in the white matter in which the micro-organisms stood out under an apochromatic lens of 20 magnifications as sharply defined tiny spots. They presented themselves under immersion in oil as small diplococci in shorter or longer chains or in colony form. They stained purple with cresyl violet and blue with methylthionine chloride, U. S. P. (methylene blue) and were gram-positive. In

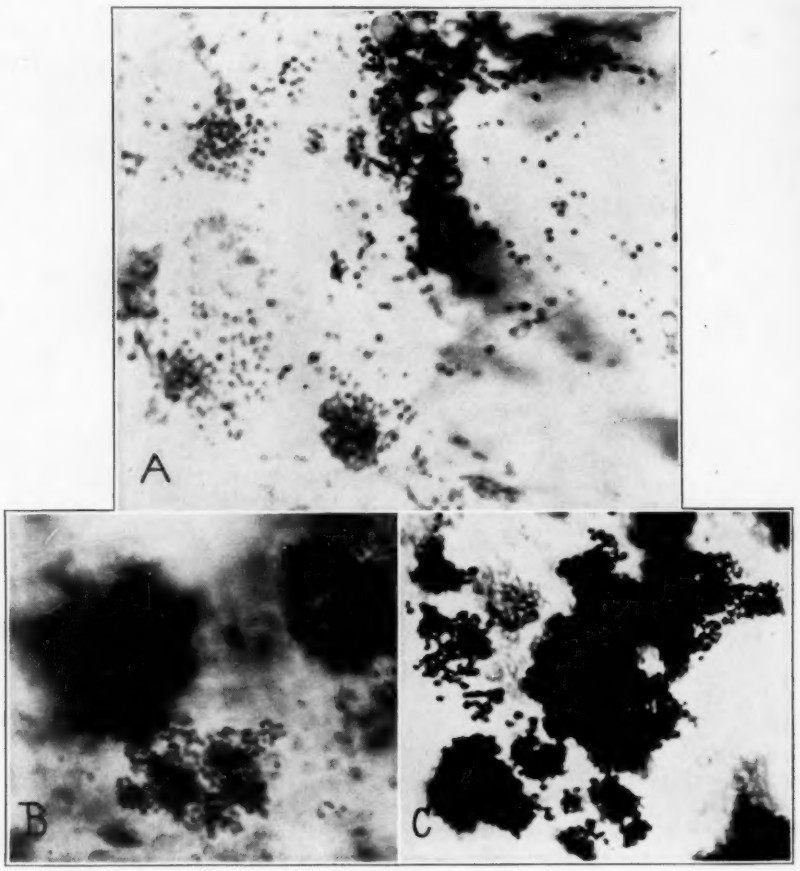

Fig. 11.—*A*, same case as in figure 3. Section showing colonies of small cocci in the form of diplococci in the corpus striatum, free in the tissue in the neighborhood of a focus of perivascular cellular infiltration. Cresyl violet stain; magnification × 1,800. *B* and *C*, same case as in figure 6. Higher magnification of colonies photographed in figure 8. *B*, cresyl violet stain; *C*, Gram's stain; magnification × 1,400.

hematoxylin-eosin preparations they stained indistinctly. They measured approximately from 0.6 to 1 micron. In the majority of cases they were found either in the edematous meshes of the pia-arachnoid or near or within the wall of smaller arteries which were surrounded with loose, edematous tissue. Occasionally, isolated larger forms were encountered (fig. 11 *A*).

In three cases (not recorded in the preliminary report) micro-organisms were observed within foci of inflammatory reaction. In two cases they were seen in the form of many small, agglutinated colonies within the necrotic center of a large glial nodule with fragmented nuclei and dark-staining shrunken forms (Stern method). Or they were seen as dark blue-staining emboli in colony form in the center of smaller blood vessels which were surrounded by proliferated glia (fig. 11, *B* and *C*). In the third case smaller colonies were seen in the edematous perivascular spaces, intermingled with lymphocytes and plasma cells.

These micro-organisms were somewhat smaller than those free in the tissue, which have already been described. They were small round cocci, measuring from 0.3 to 0.6 micron, in the form of diplococci or short chains. They stained purple with cresyl violet and were gram-positive.

COMMENT

The histologic picture presented the same features that have been described in other epidemics of epidemic (lethargic) encephalitis. The meningitis was always relatively mild; it was disseminated and was most pronounced at the base of the midbrain and within the sulci of the cerebellum. The disseminated encephalitis was not only a polioencephalitis: Although the gray masses of the brain stem showed a more marked inflammatory reaction, foci of glial proliferation and perivascular cellular infiltration were present also in the corona radiata and in the cerebellar peduncles. These observations are somewhat unusual, when compared with von Economo's description of the average case. He emphasized that there was a sharp limit between the diseased gray matter and the normal white matter. He admitted, however, that this rule cannot always be applied, since he saw cases in which the inflammation involved both the gray and the white matter. The histologic picture in other American epidemics [4] presented essentially the same features as those described in the St. Louis epidemic; involvement of the white matter seemed to be the rule (Ayer).

The mode of distribution of the inflammation (table 2) shows predilection for the gray masses of the thalamencephalon and midbrain, especially of the substantia nigra. The fact that, clinically, meningitis manifested itself first and that, histologically, this was most pronounced at the base of the brain, especially in the interpeduncular fossa, suggests a possible spread of the infection along the pial sheaths of the larger vessels into the brain itself (fig. 2). It should be emphasized that in none of the cases studied did the roots of the cranial nerves (three to twelve) show inflammation.

The presence of micro-organisms in areas which did not show inflammatory reactions may easily be explained as nonspecific agonal

4. Association for Research in Nervous and Mental Disease: Acute Epidemic Encephalitis [Lethargic Encephalitis]; An Investigation by the Association, New York, Paul B. Hoeber, Inc., 1921, vol. 1.

or postmortem invasion, or even, as has been suggested by some, as a contamination caused by air, favored by the hot weather and delay in the fixation of the brains. The presence of colonies of small cocci as diplococci or chains within the center of glial foci or as thrombi in blood vessels surrounded by a necrotic area and inflammation, however, must be considered as proof of an intra vitam infection of the brain with those micro-organisms. The problem of their specific etiologic significance, of course, cannot be solved by the pathologist. Their small size (from 0.3 to 0.6 micron), their growth in isolated colonies and their localized occurrence, however, are features that should not be overlooked by the bacteriologist when he observes on examination of small blocks of brain tissue that no micro-organisms can be demonstrated histologically and that cultures from the tissue are sterile. In attempts to transmit the disease to animals he should not be satisfied with the production of general ganglion cell disease, perivascular cellular infiltration or leptomeningitis. Only the characteristic combination of glial proliferation and perivascular cellular infiltration should be considered as histologic proof of a successful transmission.

SUMMARY AND CONCLUSIONS

The central nervous system of patients who died of encephalitis during the recent St. Louis epidemic were studied histologically. They were affected by acute disseminated encephalitis and myelitis, accompanied by mild leptomeningitis. The inflammatory reaction consisted of perivascular infiltration by small round cells and a few plasma cells and of the formation of isolated foci of proliferated glia.

Both the gray and the white matter were involved, but the nuclear masses of the thalamencephalon and midbrain were more affected than either the cortex or the rest of the brain stem.

In each case small cocci in the form of diplococci or chains were demonstrated free in the tissues, a fact which might be explained as an agonal or postmortem infection. In three cases, however, colonies of small cocci, measuring from 0.3 to 0.6 micron, were observed within foci of proliferated glia, within thrombosed blood vessels or intermingled with the perivascular cellular exudate. They formed diplococci and short chains and were gram-positive.

ENCEPHALOMALACIA IN INFANTS

(VIRCHOW'S INTERSTITIAL ENCEPHALITIS)

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Cerebral softening in infants, considered by some since the days of Virchow to be a peculiar form of encephalitis, is not uncommon. As extensive studies of recent years have shown, trauma at birth is the important, if not the only, underlying factor, in contrast to vascular lesions (thrombosis, embolism and the like), so frequent in cerebral softening in adults. Though marked softening was present in the two cases reported here, no history of trauma at birth was elicited.

REPORT OF CASES

CASE 1.—*History.*—A white female infant, aged 7 weeks, was brought to the Research and Educational Hospitals of the University of Illinois on Sept. 12, 1930, because of restlessness, sleeplessness, constipation and dyspnea on crying. She was born at term, was apparently normal at birth and was breast fed.

Examination.—The infant was fairly well nourished and not acutely ill. The scalp was normal. The left parietal bone seemed to be somewhat depressed. The fontanels showed normal pressure. There was slight ptosis of the left eyelid. The pupils were equal and reacted to light. Nystagmus was not observed. The neck was not rigid. The ears, pharynx, heart and lungs were normal. The liver and spleen were slightly palpable. The extremities were spastic, but there was no loss of function. The grip of the fingers was strong, and the patient had good use of the arms and legs. All of the deep reflexes were questionable. The baby had attacks of athetoid movements with hypertension and spasticity of the extremities, but was apparently normal between the attacks.

Laboratory observations: The urine was normal. The Wassermann reaction of the blood was negative. The hemoglobin was 70 per cent; the red cells numbered 4,100,000, and the white cells, 10,350. The differential count showed: lymphocytes, 53 per cent; large mononuclears, 7; polymorphonuclears, 38; eosinophils, 2. Roentgen examination revealed a suggestion of a large thymus.

Course.—On September 20, the following note was made by Dr. H. Beard of the department of ophthalmology: "The mother noticed a yellow color in the pupil of the left eye two or three weeks after birth. On examination, the eyeballs were very small; the pupils were dilated, revealing a yellowish, vascular mass filling the region behind the lens; the vitreous of the right eye was clouded, but no mass was made out. A diagnosis of glioma of the left eye was made, and

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From the laboratory of neuropathology of the University of Illinois, College of Medicine, Dr. Hassin, Director.

enucleation of the bulb was advised. This was done three days later. The postoperative course was uneventful. On October 2, bronchopneumonia developed, and the child died on October 8.

Necropsy (Dr. Milles).—The anatomic diagnosis was confluent bronchopneumonia of the right upper pulmonary lobe and a surgically enucleated left eye.

Brain: The dura was markedly adherent to the calvarium; the pia-arachnoid over the middle third of the right hemisphere was edematous. The underlying brain tissue was depressed, soft and fluctuant. After fixation in formaldehyde it was noted that the meninges over both of the right parieto-occipital lobes and the chiasm were opaque and blood-tinged. The right hemisphere was atrophied. In the right fronto-parietal lobe was a focus, measuring 1.5 by 2.5 cm., in which the

Fig. 1 (case 1).—Large cavity involving the cortex and white matter. Toluidine blue stain; × 5.

cortex and white matter were replaced by a weblike structure and covered by meninges. This cystlike structure extended to the occipital lobe, which also showed a weblike structure, though it was much less marked. Another focus was present in the left parieto-occipital lobe. In the left lateral ventricle a hemorrhagic clot involved the choroid plexus. The spinal cord revealed no macroscopic changes.

Microscopic Examination: Under a low magnification the disintegrated areas were seen to consist of numerous cavities more or less filled with gitter cells. Some cavities were almost devoid of cell elements. They varied in size. The larger cavities extended from the white matter to the meninges and involved extensive areas of the cerebral substance, which was completely destroyed (fig. 1). In others, remnants of cortical substance were reduced to threads (figs. 2 and 3*b*), or small islands of white matter (figs. 2 and 3*d*) were the only vestiges of cerebral tissue in a mass of scattered gitter cells and congested blood vessels (fig. 3*c*).

Fig. 2 (case 1).—Extensive softenings and lacunae of the occipital lobe. Toluidine blue stain; × 5.

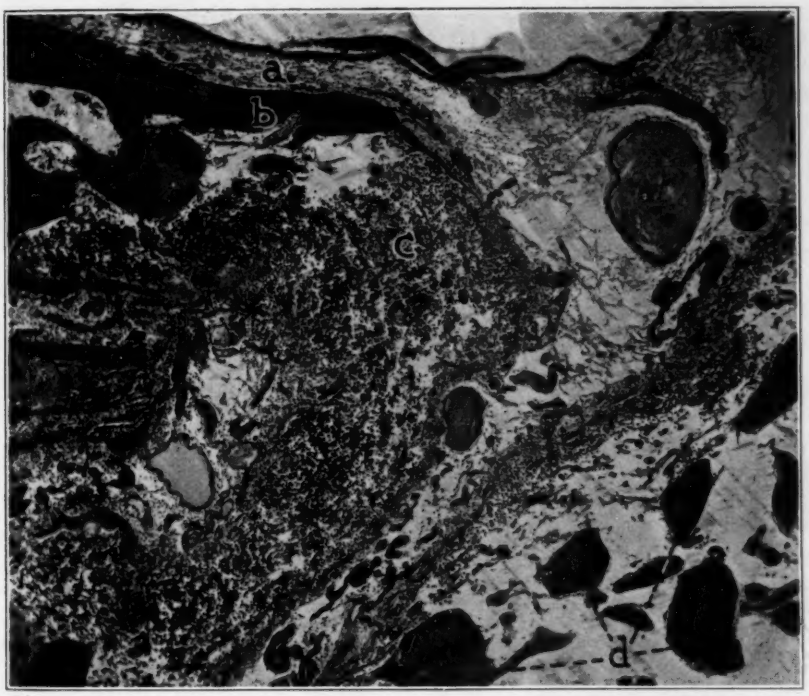

Fig. 3.—High magnification of figure 2: *a*, pia-arachnoid; *b*, cortex reduced at the right to a thread; *c*, masses of gitter cells and congested blood vessels; *d*, islands of white matter. Toluidine blue stain; × 24.

Aside from the cavities, there were also diffuse and circumscribed foci of softenings scattered in the cortex and white matter of both hemispheres and in the optic thalamus. These foci, like the cavities, consisted of dense collections of gitter cells, some of which were of large size and all of which were packed with lipoids (scarlet red stain); many were within dilated perivascular lymph spaces. Some foci were in the process of repair; they contained newly formed capillaries, fibroblasts and young connective tissue fibrils. The brain substance adjacent to the various foci and cavities showed a striking state of rarefaction—status spongiosus. The ganglion cells were reduced in numbers; in some chromatolysis was marked, even in areas not affected, whereas other cells appeared as shadows or were shrunken. Scattered throughout the white matter were numerous protoplasmic glia cells, and there was an increase in the fibrous astrocytes. The oligodendroglia or glia nuclei were swollen and increased in number. In addition, in the deeper portion of the white matter and subependymal areas and around the ventricles there were collections of glia cells which formed foci that resembled glial nodules, with an occasional gitter cell. The blood vessels were greatly congested; their adventitial spaces were dilated as the result of edema; the capillaries were prominent and proliferated. In Weigert preparations, the U-fibers (short association fibers) in the affected areas were greatly diminished. In the optic thalamus and within some of the smaller foci of softening there were considerable deposits of calcium salts.

The meninges over the cavities were hyperplastic and thickened. Their meshes were for the most part greatly distended and edematous. The arachnoid was lined by several layers of mesothelial cells. Scattered through the subarachnoid space were numerous fibroblasts, red blood cells, polyblasts, large lymphocytes, gitter cells and macrophages. The blood vessels were greatly congested; some were packed with polymorphonuclear leukocytes.

The optic chiasm contained many thickened and proliferated blood vessels. The adventitial layers were hypertrophied, owing to the presence of numerous proliferated adventitial cells. There was also an increase in glial elements, especially in the form of cytoplasmic glia. In some areas the nerve fibers were reduced in numbers.

The central canal of the spinal cord was greatly dilated and was filled with a granular fluid substance which contained a few lymphocytes, macrophages and gitter cells (fig. 4). The gray matter appeared normal, and the ganglion cells were well preserved. Cavities or softening were not present in either the gray or the white matter, but moderate edema was common. There was an increase in the oligodendroglia. The blood vessels were prominent and congested; their walls were thickened; some capillaries showed evidence of proliferation. The pia-arachnoid was hyperplastic and contained in its distended meshes a number of lymphocytes, macrophages and gitter cells. All of the blood vessels of the meninges were congested, and their walls were thickened.

Eyes (Dr. H. Beard).—Left Eye: The bulb measured 16 mm. in diameter; the cornea, 8 by 8.5 mm.; the anterior chamber was shallow; the pupil measured 2.5 mm.

Microscopic examination of horizontal sections of the bulb showed marked ingrooving in the region of the limbus, suggestive of traction from within. There was a complete, umbrella-like detachment of the retina, which was drawn together into a dense mass behind the lens, to which it was attached by a thick sheet of fibrous connective tissue. This tissue connected the ciliary body of one side to that of the other, pulling strongly inward. Shrinkage of the membrane was the

cause of the ingrooving noted. The posterior layers of the lens were cataractous, and the subretinal space was filled with an acidophilic, almost hyaline material (blood serum) containing several large masses of erythrocytes. No signs of active inflammation were present except a considerable hyperemia of the blood vessels of the uvea. The vitreous was not present. The posterior surface of the iris was tightly adherent to the lens.

Right Eye: The bulb of the right eye measured 18 by 19 by 19 mm., and showed no external abnormalities.

Microscopic examination of horizontal sections showed multiple, closely packed infoldings of the retina in the temporal side just behind the ora serrata. The

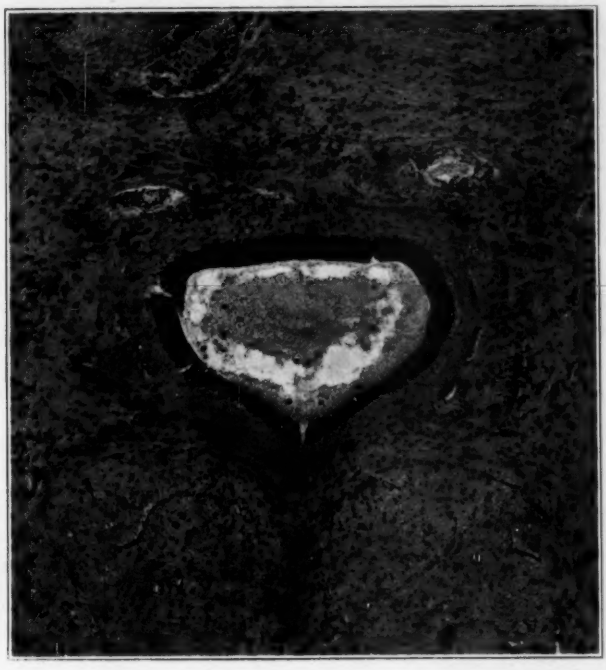

Fig. 4 (case 1).—Spinal cord showing dilated central canal filled with various cells described in the text. Toluidine blue stain; × 75.

folds were drawn forward and inward to become attached to the posterotemporal surface of the lens by newly organized fibrous tissue. Between some of the folds (between their rod and cone surfaces) were hyaline inclusions, staining deeply purple. The inclusions were surrounded by scattered leukocytes and plasma cells, many of which were necrotic. The retina was not elsewhere detached. The ciliary body, iris and optic nerve were normal.

The findings could be interpreted only on the basis of a prenatal, intra-ocular inflammatory process which had healed before the eyes were brought to necropsy. Their small size showed arrested development. The formation of organized membranes in the region of the ciliary body indicates clearly the precedence of a plastic iridocyclitis. The membranes caused the retinal detachment in both eyes by the familiar process of traction due to shrinkage. Undoubtedly the process was of

septic metastatic maternal origin, though it does not seem possible to determine from anatomic study alone just what organism was responsible. There was little to suggest one of the infectious granulomas, and it seems rational to indict one of the commoner pyogenic organisms. The case was a variety of pseudoglioma—in reality a healed, prenatal iridocyclitis with retinal detachment.

Summary.—An infant, aged 7 weeks, had attacks of athetoid movements with hyperextension and spasticity of all extremities. The date of onset of the attacks is not known. However, ocular changes were noted several weeks after birth; these showed arrested development, microphthalmia, prenatal iridocyclitis and retinal detachment. In the brain were extensive foci of softening, cavities, atrophy of the right hemisphere and a reactive, aseptic meningitis. The cavities or lacunae, marked status spongiosus and proliferative phenomena in the glia indicated an advanced softening, which evidently was present at birth. A history of trauma incident to birth (difficult or prolonged labor, instrumentation or the like), however, was not obtained.

Case 2.—*History* (Dr. B. I. Beverly).—A male infant, aged 3½ months, was admitted to the Children's Memorial Hospital on May 27, 1926, because of diarrhea (six watery stools a day) and a convulsion on the day before admission. Birth was normal; the child was breast fed for one month; a condensed milk was given thereafter. The family history was without significance.

Examination.—The throat was red. There were general clonic and generalized convulsions. A blood count revealed: red cells, 2,940,000; platelets, 100,000; white cells, 25,400. The differential count was: polymorphonuclears, 45; small lymphocytes, 12; large lymphocytes, 36 per cent. The bleeding time was fourteen minutes. A spinal puncture gave negative results. Fifty cubic centimeters of blood was given intramuscularly.

Course.—On May 30, the child was stuporous; the fontanels were bulging; the knee jerks were lively, and the neck was rigid. A spinal puncture on May 31 revealed: Pandy test, +; Wassermann reaction, negative; sugar, 52 per cent; cells, 190. On June 11, the blood platelets numbered 240,000, and the bleeding time was four minutes. A spinal puncture gave a bloody fluid. On June 12, there were generalized twitchings. On June 15, by subdural puncture, 3 cc. of clear fluid was obtained; it contained 116 cells. On June 18, spinal puncture yielded fluid containing 6 cells; the Pandy test was negative. The child was sent home in a good condition.

On June 27 the patient was readmitted. Vomiting had appeared on the preceding day, and there had been from five to six stools. Convulsions and death occurred on June 28.

Necropsy.—Anatomic diagnosis revealed marked edema of the leptomeninges; hyperemia and edema of the brain; cloudy swelling of the myocardium, liver and kidneys; moderate fatty change of the liver; hyperemia and edema of the lungs; hyperemia of the mesenteric lymph nodes; fibrinopurulent right otitis media.

After fixation in formaldehyde the sectioned brain showed numerous foci of softening in the cortex of the frontal, parietal, temporal and occipital lobes. None was evident in the cerebellum or the basal ganglia. One focus of softening was present in the posterior corpora quadrigemina.

Microscopic Examination: The outstanding pathologic features were marked, irregular areas of softenings, which were more or less diffuse, but were present mainly in the cortex (fig. 5). In some instances they were present also in the subcortex, where they were mostly multiple. Lacunae or cavities were few and,

in contrast to case 1, minute. The softened areas, lacunae and cavities contained numerous gitter cells, which when stained with scarlet red were found to be packed with fat; these cells surrounded the blood vessels, which were greatly congested. In many instances the blood vessels were thickened; the capillaries were proliferated and intermingled with strands of fibroblasts. Some foci contained extensive deposits of calcium salts in and among the ganglion cells, which were greatly degenerated and altered. The cells were considerably reduced in number

Fig. 5 (case 2).—Foci of softening in the cortex of the occipital lobe. Toluidine blue stain; × 30.

and in some areas were completely destroyed. The adjacent white matter and the subpial cortical layer were markedly rarefied (status spongiosus) and contained numerous protoplasmic glia cells (fig. 6). Elongated or sausage-shaped cells (rod cells, microglia), *gemästete* glia cells and gitter cells were also present throughout the white matter. The blood vessels also exhibited proliferative phenomena in their adventitial and endothelial layers. Newly formed capillaries were frequently observed.

Areas of the brain which did not show any of the foci of softenings were also more or less affected. Edema was marked, and a glial reticulum was more or less in evidence. The blood vessels were hyperemic and the capillaries prominent and

proliferated. The ganglion cells exhibited degenerative changes, among which chromatolysis was the rule. Many of the cells and their processes showed swelling; others were shrunken or atrophied. Neuronophagia was absent. The histologic picture was not unlike that seen in so-called toxic encephalitis, but it was milder.

Examination of the meninges showed that the pia-arachnoid was distended, edematous and hemorrhagic in spots. The blood vessels were hyperemic. In some

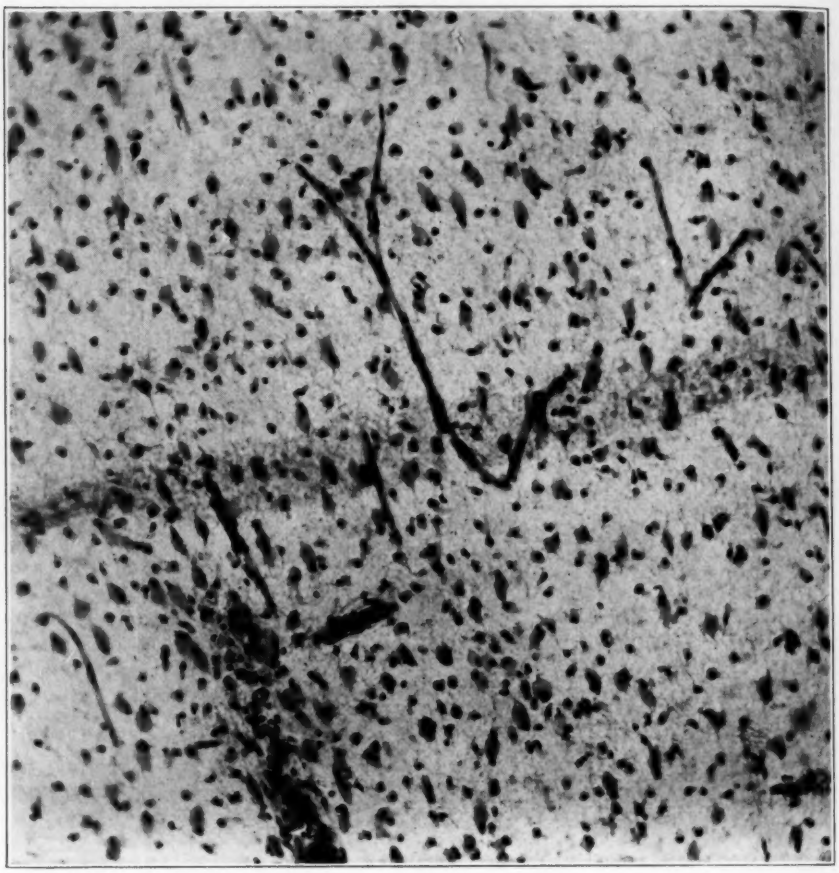

Fig. 6 (case 2).—Cytoplasmic glia, proliferated capillaries and marked glial reticulum. Toluidine blue stain; × 180.

portions reactive phenomena were pronounced. Fibroblasts were especially numerous. The meshes contained also a number of polyblasts, lymphocytes, macrophages and gitter cells.

Summary.—An infant, aged 3½ years, suddenly became ill with diarrhea and convulsions, rigidity of the neck and generalized twitchings. The spinal fluid contained 190 cells; leukocytosis was present. The symptoms disappeared within three weeks. Eight days later a relapse set in, with vomiting, diarrhea and convulsions; death followed within two days.

Histologic examination of the brain revealed diffuse and circumscribed foci of softening, lacunae and small cavities filled with gitter cells, and changes in the ganglion cells with reactive phenomena of the glia, meninges and blood vessels.

COMMENT

The lesions in the two cases are similar, though they vary in degree. In case 1 there was a rather advanced stage of softening, as evidenced by the large lacunae and empty cavities. In case 2, the process was more recent. This difference was evident also in the clinical picture, which was acute and stormy. The fatty change of the liver and cloudy swelling of the myocardium, kidneys and liver would point to toxemia as the cause. The etiology was even more obscure in case 1. Since the changes in the eye in this case were regarded as prenatal, of inflammatory, i. e., toxic-infectious character, the softening of the brain was also most likely prenatal, due to the same infection that affected the eye.

Mention should be made here of the collections of glia cells in the deep layers of the white matter and the subependyma and around the ventricles in case 1. These foci were regarded by Ranke [1] in cases of retarded development as germinal centers (*Keimreste*). Ranke found them in cases of congenital syphilis, porencephaly and microphthalmia. His findings were confirmed by Schwartz,[2] Wohlwill,[3] Gohrbandt [4] and others. Ceelen [5] believed that they were inflammatory in nature. Recently, Alpers [6] described similar foci in a case of progressive degeneration of the gray matter. The germinal foci in case 1, therefore, may be similarly explained, as microphthalmia and a prenatal iridocy-

1. Ranke, O.: Beiträge zur Kenntnis der normalen und pathologischen Hirnrindenbildung, Beitr. z. path. Anat. u. z. allg. Path. **47**:51, 1910.

2. Schwartz, P.: Die Ansaugungsblutungen im Gehirn Neugeborener, Ztschr. f. Kinderh. **29**:102, 1921; Die Geburtsschädigungen des Gehirns und die Virchowsche Encephalitis interstitialis neonatorum, Centralbl. f. allg. Path. u. path. Anat. **32**:57, 1921; Erkrankungen des Zentralnervensystems nach traumatischer Geburtsschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:263, 1924; Die Verfettungen im Zentralnervensystem Neugeborener, ibid. **100**:713, 1926; Die traumatischen Schädigungen des Zentralnervensystems durch die Geburt; anatomische Untersuchungen, Ergebn. d. inn. med. u. Kinderh. **31**:165, 1927. Schwartz, P., and Fink, L.: Morphologie und Entstehung der Geburtstraumatischen Blutungen in Gehirn und Schädel des Neugeborenen, Ztschr. f. Kinderh. **40**:427, 1926.

3. Wohlwill, F.: Zur Frage der sogenannten Encephalitis congenita (Virchow), Ztschr. f. d. ges. Neurol. u. Psychiat. **68**:384, 1921.

4. Gohrbandt, E.: Ueber Gehirnbefunde bei Neugeborenen und Säuglingen, Virchows Arch. f. path. Anat. **247**:374, 1923.

5. Ceelen, W.: Ueber Gehirnbefunde bei Neugeborenen und Säuglingen (Encephalitis congenita Virchows), Virchows Arch. f. path. Anat. **227**:152, 1919.

6. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. **25**:469 (March) 1931.

clitis were present, the cause of which was some infection or toxemia during intra-uterine life. The extensive softenings evidently followed.

The conditions in the brains of infants here outlined were first described by Virchow [7] under the name of encephalitis congenita. The principal changes were circumscribed and diffuse collections of gitter cells and fat droplets in the white, rarely in the gray, matter, which he regarded as a fatty metamorphosis of the neuroglia. He considered the condition to be an active irritative process caused by an inflammation. The inflammatory nature was disputed by Hayem,[8] while Parrot [9] regarded malnutrition as the cause. In the cases of von Graefe [10] and Hirschberg [11] the condition was associated with corneal ulcers. Of interest is the view of Jastrowitz,[12] who denied that the condition was entirely pathologic. He looked on the diffuse changes in the white matter as physiologic, and ascribed to the gitter cells the function of the building up of myelin. Only when the lesions were circumscribed and involved the gray matter and the basal ganglia was the process, in his opinion, pathologic. This view was accepted by Boll,[13] Eichhorst,[14] Flechsig,[15] Merzbacher,[16] Ceelen, Wohlwill, Guillery,[17] Scheyer [18] and others. Some of these authors recognize two types of gitter cells: the so-called *Abräumzellen*, which are invariably present in certain degenerative conditions of the nervous system, and *Aufbauzellen*, the

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7. Virchow, R.: Congenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129, 1867; Ueber interstitielle Encephalitis, ibid. **44**:472, 1867; Encephalitis congenita, Berl. klin. Wchnschr. **46**:705, 1883

8. Hayem, G.: Sur les diverses formes d'encéphalite, Paris, A. Delahaye, 1868, p. 79.

9. Parrot: Arch. de physiol. norm. et path. **1**:530, 1868.

10. von Graefe: Hornhautverschwärung bei infantiler Encephalitis, Arch. f. Ophth. **12**:250, 1867.

11. Hirschberg: Berl. klin. Wchnschr. **31**:327, 1868.

12. Jastrowitz, M.: Studien über die Encephalitis und Myelitis des ersten Kindesalters, Arch. f. Psychiat. **2**:389, 1870; **3**:162, 1872.

13. Boll, F.: Die Histologie und die Histiogenese der nervösen Zentralorgane, Arch. f. Psychiat. **4**:1, 1874.

14. Eichhorst, H.: Ueber die Entwicklung des menschlichen Rückenmarks und seiner Formelemente, Virchows Arch. f. path. Anat. **67**:424, 1875.

15. Flechsig, P.: Die Leitungsbahnen im Gehirn und Rückenmark des Menschen, Leipzig, W. Engelmann, 1876.

16. Merzbacher, L.: Untersuchungen über die Morphologie und Biologie der Abräumzellen im Zentralnervensystem, Histol. u. histopath. Arb. ü. d. Grosshirnrinde **3**:1, 1909.

17. Guillery, H., Jr.: Entwicklungsgeschichtliche Untersuchungen als Beitrag zur Frage der Encephalitis interstitialis neonatorum (Virchow), Ztschr. f. d. ges. Neurol. u. Psychiat. **84**:205, 1923.

18. Scheyer, H. E.: Ueber Fettkörnchenzellbefunde im Rückenmark von Föten und Säuglingen, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:185, 1925.

rôle of which is supposed to be the building up of myelin; i. e., they are physiologic. Merzbacher even subdivided the latter into nine morphologic types, which he classified as embryonic *Aufbauzellen*. The process of myelinization is supposed to begin at about the fifth month of fetal life and to be completed at about the eighth month after birth. However, since gitter cells are present practically only in degenerative conditions, it seems illogical to impute to them a double function. Therefore, considerable controversy and with it a large amount of literature arose on this subject. I shall refer merely to the noteworthy contributions by Schwartz, who has shown that frequently, though this is not the exclusive cause, trauma of the brain at birth is the cause of the presence of gitter cells in the condition under discussion.

Schwartz' observations have been confirmed by Siegmund,[19] Dollinger,[20] Sternberg,[21] Rydberg [22] and others. According to Schwartz, the brain is subject to damage during parturition even in the absence of difficult or instrumental delivery. He considered that the cause lies in the difference between the atmospheric pressure and that of the uterine cavity. This difference produces an effect like that of suction; it causes circulatory disturbances, congestion and rupture, with minute hemorrhages which are followed by softening. If the infant survives, cysts may form, with porencephaly and sclerosis (Schwartz, Schultz,[23] Schminke [24] and others) or even more profound destruction, as, for instance, in the case of Limbeck,[25] in which the brain of an infant, aged 4 days, was transformed into a bag. Injury of the pregnant mother was given as the cause in a case by Seitz; [26] during the sixth month

19. Siegmund, H.: Geburtsschädigungen des kindlichen Gehirns und ihre Folgen, München. med. Wchnschr. **70**:137, 1923; Die Entstehung von Porencephalien und Sklerosen aus Geburtstraumatischen Hirnschädigungen, Virchows Arch. f. path. Anat. **241**:237, 1923.

20. Dollinger, A.: Geburtstrauma und Zentralnervensystem, Ergebn. d. inn. Med. u. Kinderh. **31**:373, 1927.

21. Sternberg, C.: Multiple Höhlenbildungen im Grosshirn (Markporencephalien) als Folgen des Geburtstrauma, Beitr. z. path. Anat. u. z. allg. Path. **84**:521, 1930.

22. Rydberg, Erik: Cerebral Injury in New-Born Children Consequent on Birth Trauma, Acta path. et microbiol. Scandinav., supp. 10, 1932. p. 1.

23. Schultz, A.: Drei Fälle von Geburtsläsionen des Gehirns mit Entstehung von Sklerosen und Erweichungscysten; Beitrag sur Frage der Fettkörnchenzellen im neugeborenen Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:638, 1925.

24. Schminke, Alex: Encephalitis interstitialis Virchow mit Gliose und Verkalkung, Virchows Arch. f. path. Anat. **60**:290, 1920.

25. Limbeck: Encephalitis congenita und Porencephalie, Ztschr. f. Heilk. **7**:2, 1886.

26. Seitz, Ludwig: Ueber die durch intrauterine Gehirnhemorrhagien entstandenen Gehirndefekte und die Encephalitis congenita, Arch. f. Gynäk. **83**:701, 1907.

of gestation the mother fell down a flight of stairs on two occasions; the premature infant died five hours after spontaneous delivery; the brain revealed extensive softening and cavities.

Some authors (Dahlmann,[27] Meier [28] and others) have held that arterial spasm, with resultant anemic infarction, is probably the cause of the softening. Other causes than trauma, such as infections, sepsis, toxemias and similar conditions, either in the mother or in the infant, were reported by Fischl,[29] Gohrbandt, Dollinger and others.

Thus in cases of softening of the brain in infants the causes that have been given are trauma, vascular disturbances, infections and intoxications. In my two cases, neither trauma nor vascular disturbance was the cause. The cause in case 1 was evidently an infection, and in case 2 a toxemia. Both may produce organic lesions, not only in the brain but also in the spinal cord. The remarkable work of Rosenthal [30] and Lotmar [31] proved that the central nerve tissues may be directly affected by toxins and become softened or necrosed, depending on the degree of the infection or intoxication and on the age and resistance of the animal. Evidently the brains of infants are less resistant to severe intoxication or infection; for this reason probably they show more extensive destruction than do the brains of adults under similar conditions. The infants that survive may exhibit in later life various signs, such as convulsions, paralysis, spasticity, athetosis and idiocy, which may be traced to the aforementioned lesions in the central nervous system in the new-born (Köppen,[32] Probst [33] and others).

CONCLUSIONS

1. Cerebral softening in infants is considered most commonly to be due to trauma at birth.

2. Infection (case 1) and intoxication (case 2) must also be considered as etiologic factors.

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27. Dahlmann, A.: Beitrag zur Kenntnis der symmetrischen Höhlen im Grosshirnmark des Säuglings mit Bemerkungen über Entstehung von Hirnhöhlen im Allgemeinen, Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:323, 1910.

28. Meier, Ernst: Ueber einen Fall von totaler Erweichung beider Grosshirnhemisphären bei einem fünf Monate alten Kinde, Jahrb. f. Kinderh. **76**:552, 1912.

29. Fischl, R.: Zur Kenntnis der Encephalitis beim Säugling, Jahrb. f. Kinderh. **49**:58, 1899.

30. Rosenthal, S.: Experimentelle Studien über amöboide Umwandlung der Neuroglia, Histol. u. histopath. Arb. ü. d. Grosshirnrinde **6**:89, 1913.

31. Lotmar, Fritz: Beiträge zur Histologie der akuten Myelitis und Encephalitis, sowie verwandter Prozesse, Histol. u. histopath. Arb. ü. d. Grosshirnrinde **6**:248, 1913.

32. Köppen, M.: Ueber Gehirnkrankheiten der ersten Lebensperioden, als Beiträge zur Lehre von Idiotismus, Arch. f. Psychiat. **30**:896, 1898.

33. Probst, M.: Ueber durch eigenartigen Rindenschwund bedingten Blödsinn, Arch. f. Psychiat. **36**:762, 1903.

ETIOLOGY OF EPILEPSY

WITH SPECIAL REFERENCE TO ITS OCCURRENCE IN TWINS

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Several years ago we undertook to collect material for a study of mental disorders in twins. A preliminary report of this study was read before the California Medical Association in 1931.[1] In that report are given a general plan of the study and a tabulated summary of the findings in 127 pairs of twins with mental disorders which had been accumulated up to that time.

Since then the work of collecting the material has been completed. We now have in our possession case records of 1,011 pairs of twins (including 8 sets of triplets) with mental disorders and a control group of 308 pairs of normal twins. This material is now being analyzed and prepared for publication. In the collection are included 107 pairs of twins with epilepsy. The object of this communication is twofold: first, to present an analysis of this group of cases, and second, to utilize this and other material in a study of the etiology of epilepsy.

GENERAL SURVEY OF THE MATERIAL

Only a few cases of epilepsy in twins have been reported in the medical literature. These have been summarized and tabulated by Siemens,[2] Lange[3] and Luxenburger.[4] We have found some case reports which were overlooked by these writers and have added some that have

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1. Rosanoff, A. J.: Twins: A Study of Certain Mental Disorders: Preliminary Report, California & West. Med. **37**:101 (Aug.) 1932.

2. Siemens, H. W.: Die Zwillingspathologie, Berlin, Julius Springer, 1924.

3. Lange, J., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1928.

4. Luxenburger, H.: Psychiatrisch-neurologische Zwillingspathologie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **56**:145, 1930.

been reported since the publication of Luxenburger's paper in 1930.[5] The resulting collection of cases, 35 in all, is summarized in table 1.

These cases constitute, for the most part, a specially selected group. In connection with epilepsy, as with other pathologic conditions, physicians seem to find cases of twins in which both are affected by the condition in question of greater importance and more worth reporting than if only one of the twins is affected. Hence there is, by comparison with our series of cases, presented in table 2, a relatively greater number of such instances.

Physicians seem also to find cases in monozygotic twins of more interest than those in dizygotic twins. Hence there is also an overloading of the material in table 1 with cases of that type—which constitute here over two thirds of the ascertained cases. In nearly one fourth of the cases reported in the literature the type of twins, i. e., whether monozygotic or dizygotic, is unascertained, showing that the fundamental

TABLE 1.—*Epilepsy in Twins Reported in the Literature*

Type of Twins	Number of Cases	One Affected	Both Affected
Monozygotic	19	6	13
Dizygotic	8	7	1
Type unascertained	8	4	4
Totals	35	17	18

significance of this kind of material was not borne in mind by many of the observers reporting the cases.

The mere fact of the meager total amount of such material published in the literature, when so much of it can easily be found, also shows a failure on the part of physicians to appreciate the value of such material from the standpoint of the light that it can throw on the etiology of epilepsy.

In connection with our study, the aim was to collect cases of mental deficiency, epilepsy, psychoses, criminality and allied conditions in twins in sufficiently large numbers to make possible a statistical treatment. We have sought to accumulate an unselected series, regardless of whether one or both of the pair are affected and regardless of the type of twins.

The unsuitableness for statistical treatment of the case reports of neuropsychiatric conditions in twins to be found in the literature has recently been emphasized by Luxenburger,[4] not only by reason of the

5. (*a*) Toledo, R. M.: Notes on Two Cases of Epilepsy in Twins, with Photographs, J. Ment. Sc. **65**:262 (Oct.) 1919. (*b*) Whitney, E. A.: Microcephaly in Twins, M. J. & Rec. **130**:158 (Aug. 7) 1929. (*c*) Olkon, D. M.: Epilepsy of the Angiospastic Variety in Monozygotic Twins, Arch. Neurol. & Psychiat. **25**:1111 (May) 1931. (*d*) LeGras, A. M.: Psychose en Criminaliteit bij Tweelingen, Utrecht, Kemink en zoon N. V., 1932. (*e*) Sanders, J.: Zwillinge mit Epilepsie, Genetica **15**:67, 1933.

insufficient total amount of such material that is available but also by reason of its biased selection, as has already been shown.

Nevertheless the reported cases of epilepsy in twins, as summarized in table 1, reveal two important facts which, as we shall show, are borne out by our material as well, namely: (*a*) that in a considerable proportion of monozygotic twins with epilepsy only one of the pair is affected and (*b*) that there is a significant contrast between monozygotic and dizygotic twins as to the relative proportions of cases in which only one of the pair is affected.

Our material is summarized in table 2. It may be seen at a glance that the material, unlike that presented in table 1, is practically free from overloading with the monozyotic type of twins, and, among all types. with instances of both of the pair affected. Accordingly, we find among monozygotic twins even a larger proportion of instances of only one of the pair affected—no less than 9 of a total of 23 cases, or 39.1 per cent.

TABLE 2.—*Epilepsy in Twins—New Cases*

Type of Twins	Number of Cases	One Affected	Both Affected
Monozygotic, males	9	4	5
Monozygotic, females	14	5	9
Same sex, dizygotic, males	15	12	3
Same sex, dizygotic, females	24	20	4
Opposite sex, dizygotic	45	32	13
Totals	107	73	34

As regards the contrast between monozygotic and dizygotic twins, we find it greatly reduced by comparison with the figures in table 1, but nevertheless still unmistakable. The proportion of instances of only one of the pair affected among the dizygotic twins amounts to 76.2 per cent.

These findings suggest the following propositions concerning hereditary or germinal factors in the etiology of the obviously heterogeneous group of cases included under the heading of epilepsy: 1. Such factors undoubtedly exist, as is indicated by the contrast between monozygotic and dizygotic twins revealed both in table 1 and in table 2. 2. The hereditary factors are often, in themselves, inadequate for the production of epilepsy, as is indicated by the many cases of monozygotic twins in which only one of the pair is affected. 3. The hereditary factors are not invariably present—therefore not essential—in the etiology of epilepsy, as is indicated by the great proportion of cases among dizygotic twins in which both of the pair are affected. This excessive proportion is brought out most strikingly in a comparison of dizygotic twins with siblings—a matter to which more detailed reference will be made on page 1177.

These proportions are in no way out of harmony with statistics based on the many genealogical studies of epilepsy that have been made. Among the most recent studies of this type, that of Calvert Stein [6] is selected for special reference because it is based on a large amount of material (family histories of 1,000 epileptic persons) and because provision is made for comparison with a nonepileptic control group. In Stein's report seizures were found in 2.9 per cent of the parents, in 4.1 per cent of the siblings and in 2.2 per cent of the offspring of epileptic persons. The corresponding figures for the nonepileptic control group are 0.4, 0.8 and 0.9 per cent. Other studies, both American and European, such as those of Burr,[7] Thom,[8] Brain,[9] Green,[10] Küenzi [11] and Cobb,[12] have yielded similar data.

SIMILAR AND DISSIMILAR CASES IN TWINS

In reporting cases of disease observed in twins, physicians have often stressed the identicalness of the manifestations and their close coincidence in time. There can be no doubt of the authenticity of some remarkable cases of this sort, to be explained by the obvious facts of identical heredity and exposure to identical environmental conditions. However, as regards epilepsy, it should be noted that close similarity of manifestations is the rare exception; more or less marked dissimilarity is the rule, even in monozygotic twins. This is true not only of our own material but also of that reported by others, notably Luxenburger [4] and Legras.[5d]

We have selected the following case as representing the closest degree of similarity in epileptic twins to be found in our collection.

CASE 1.—*Monozygotic female twins, both affected, similarly.*

The S. twins, Margaret and Marion, were born in Clarence, Erie County, N. Y., on Jan. 29, 1919. Birth is said to have been at full term and normal; they weighed, respectively, 5¼ and 5¾ pounds (2,381.3 and 2,608.1 Gm.). Both walked at 15 months. Both had measles and whooping cough at 4 years. At 9 years

6. Stein, C.: Hereditary Factors in Epilepsy, Am. J. Psychiat. **12**:989 (March) 1933.

7. Burr, C. W.: Heredity in Epilepsy, Arch. Neurol. & Psychiat. **7**:721 (June) 1922.

8. Thom, D. A.: Epilepsy in the Offspring of Epileptics, Am. J. Psychiat. **1**: 613 (April) 1922.

9. Brain, W. R.: The Inheritance of Epilepsy, Quart. J. Med. **19**:299 (April) 1926.

10. Green, W.: Hereditary Factors in Epilepsy, as Set Forth in a Study of One Thousand Cases, J. Michigan M. Soc. **28**:749 (Nov.) 1929.

11. Küenzi, F.: Ueber das Wiederauftreten von Epilepsie unter den Nachkommen von Epileptikern, Monatschr. f. Psychiat. u. Neurol. **72**:245, 1929.

12. Cobb, S.: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245 (May) 1932.

they were both in the Buffalo General Hospital for tonsillectomy. They went to school at 7 years and were in the third grade at 9.

Epileptic seizures began in both at the age of 9 years and occurred at the rate of two or three a week. The seizures are very similar in the two. There is a vague psychic aura, which enables them to know when a seizure is about to occur; then there are some myoclonic preliminaries; the face becomes flushed, and the patient often weeps and cries; the seizures are of the grand mal type. Following a seizure they appear as if in a chill and then go to sleep for about two hours.

They were admitted to the Craig Colony for Epileptics, at Sonyea, N. Y., on April 17, 1930, and were still there in April, 1931, when this record was made. Physically they resemble each other very closely and have been judged by the physicians and others who know them to be monozygotic twins, although the conditions at birth were not ascertained. Neurologic examination gave negative results in both. Wassermann tests, made at the ages of 9 and 11 years, gave negative results.

An intelligence test (Yerkes-Bridges) was made on their admission to the colony and revealed an intelligence quotient of 71 for Margaret and 68 for Marion. In October, 1930, a Stanford achievement test was made that revealed educational ages of 9 years and 7 months and 9 years and 9 months, respectively.

In most cases in which both twins of the pair are involved there are, as has already been stated, dissimilarities in the condition. These dissimilarities are either quantitative or qualitative.

We speak of *quantitative dissimilarity* in cases in which both twins of the pair have epilepsy, but there are differences in age at onset, in frequency or severity of seizures, in remissions, in mental complications or in outcome. We speak of *qualitative dissimilarity* in cases in which one twin has epilepsy and the other some neuropsychiatric condition belonging to another clinical group, such as mental deficiency or psychotic disease.

The following case represents an instance of quantitative dissimilarity.

CASE 2.—*Monozygotic male twins, both affected, but in a manner quantitatively dissimilar.*

The T. twins, Otto and Alfred, were born in Chicago on Dec. 30, 1894. Otto began to have seizures in infancy, while teething. The seizures occurred about once a month until he was 14 years of age, when they ceased for about a year. Then they recurred and have since occurred with increasing frequency, so that at the time of this record (July, 1932) they were occurring one or more times a day and often during the night as well. Otto has had no schooling, partly by reason of the epilepsy and partly by reason of mental deficiency. He has never talked distinctly and has never been able to do any kind of work. A Stanford-Binet test, made in September, 1926, revealed an intelligence quotient of 51. As the seizures increased in frequency and severity they became complicated with psychotic manifestations; he grew excitable, destructive, antagonistic toward his brother and mother and at times violent. On Sept. 18, 1926, he was committed to the Elgin State Hospital (Ill.). In 1930 he was taken home, and remained for a little over a year, but was readmitted to the hospital in April, 1932, and is still a patient there.

Alfred's case was different. While physically the two twins were "identical in every respect," Alfred was free from epilepsy or seizures of any kind up to the age of 14 years. He was normal mentally, bright in school and reached the seventh grade, but then could not continue schooling because epilepsy had begun. The first known seizure occurred at night. After that seizures occurred with increasing frequency, often in series lasting for twenty-four hours. There developed marked irritability, especially after seizures, and finally he was committed to the Chicago State Hospital on Dec. 3, 1914. He remained there until Dec. 22, 1917, when he died in a convulsion.

The next case represents a striking instance of qualitative dissimilarity, one twin having epilepsy and the other being affected by psychotic disease.

CASE 3.—*Monozygotic female twins, both affected, but in a manner qualitatively dissimilar.*

The L. twins, Louisa and Rose, of Italian parentage, were born in Haverhill, Mass., on Aug. 6, 1909. They were "exactly alike" and often could not be told apart even at home. At the age of 14 Louisa began to have spells, during which she would lose consciousness and sometimes bite her tongue. Both twins worked in a shoe factory and Louisa had spells at the factory from time to time, and would be sent home on such occasions. Gradually she seemed to deteriorate mentally and there developed difficulties in behavior; she would go out at night with men and stay until 2 a. m.; the parents could no longer control her as she would have outbursts of temper, spit in her mother's face and threaten to turn on the gas and kill every one in the house. She was committed to the Massachusetts Reformatory for Women on May 29, 1930. An intelligence test made on admission revealed an intelligence quotient of 50. While at the Reformatory she had several epileptic seizures, in one of which she fell down a flight of stairs. On Jan. 25, 1932, on account of the seizures, she was transferred to the Monson State Hospital (for epileptic patients). At the time of this record (August, 1932) she was still a patient there, having been observed in one grand mal and two petit mal seizures since admission.

Epilepsy never developed in Rose. At first her trouble consisted in severe headaches, said to be of migrainous type, occurring just before the menstrual periods. Gradually she, too, became hard to manage, wanted to go out at night and quarreled with her parents. On one occasion she cut off her hair when her parents refused to permit her to have it bobbed. Friction with the parents increased; she became stubborn, and finally refused to go to work at the shoe factory. In the latter part of August, 1926, there suddenly developed a psychosis. An adjoining house had caught fire during the night. She was terrified and ran to the window calling "Fire!" "Police!" From that time on, psychotic symptoms persisted; she was greatly disturbed, and on September 11 was committed to the Danvers State Hospital (Mass.). There she showed rapid deterioration, both mentally and physically. A note made in the spring of 1928 stated: "Quiet, indifferent, has to be dressed, eats poorly, at times has to be tube-fed, does not answer when addressed, never speaks except to mutter to herself in Italian." She died in the hospital on May 8, 1928, of pulmonary tuberculosis. The official diagnosis of the mental condition was dementia praecox.

Dissimilarities of both sorts, quantitative and qualitative, are greater and more frequent in dizygotic than in monozygotic twins. As regards

qualitative dissimilarities, only two such instances are to be found among 14 cases of monozygotic twins in which both of the pair are affected: one case, already cited, in which the nonepileptic twin had a deteriorating psychosis (dementia praecox?), and another in which the nonepileptic twin had a tumor of the spinal cord following trauma. This case will be more fully described later (case 8).

In striking contrast, we find among 20 cases of dizygotic twins in which both of the pair are affected no fewer than 11 instances of qualitative dissimilarity. The conditions in the nonepileptic twins in these cases are distributed as follows:

	Cases
Mental deficiency	6
Mental deficiency with psychosis	1
Mental deficiency with behavior difficulty	1
Deteriorating psychosis (dementia praecox?)	1
Difficulties in behavior	1
Dementia paralytica	1

RELATIONSHIP OF EPILEPSY TO MENTAL DEFICIENCY AND TO LITTLE'S DISEASE

The traditional view that "genuine" or "idiopathic" epilepsy is a neurosis, functional in nature, is giving way under the pressure of steadily accumulating evidence which indicates rather that epilepsy is a decerebration syndrome. From this newer point of view it becomes a matter of special interest to consider the relationship of epilepsy to other decerebration syndromes, particularly mental deficiency and Little's disease.

That epilepsy is often complicated with mental deficiency is well known. This is true of extramural as well as of institutional cases, but more so of the latter, as the mental deficiency is often the main reason for seeking institutional care. Thus, among the 327 patients admitted to the Craig Colony for epileptic persons during the year ending June 30, 1932, only 79, i.e., 24.2 per cent, were rated as of normal intelligence, all the remaining patients showing mental deficiency in various degrees, as follows: idiocy, 4.6 per cent; imbecility, 24.2 per cent; moronism, 4.7 per cent.[13]

Striking as these figures are, they undoubtedly represent an understatement of the case. If slighter degrees of subnormal intelligence were counted—the cases of so-called borderline and dull normal intelligence (intelligence quotient from 70 to 89)—then over 90 per cent of institutional cases of epilepsy would be found to be complicated with mental deficiency.

It has also long been known that epilepsy is often associated with Little's disease. According to Spratling,[14] for example, 11 per cent of his series of 1,070 eases of epilepsy were associated with infantile cerebral palsy, while, inversely,

13. Forty-Fourth Annual Report of the Department of Mental Hygiene, July 1, 1931, to June 30, 1932, Albany, N. Y., 1933.

14. Spratling, W. P.: Epilepsy and Its Treatment, Philadelphia, W. B. Saunders Company, 1904.

"40 per cent of all cerebral hemiplegias of infancy ultimately become epileptic." Perhaps these figures, too, are an understatement of the case, for slight residual cerebral palsies can be readily overlooked in the course of routine neurologic examinations in a large state institution.

A relationship between epilepsy and mental deficiency can be demonstrated not only by their frequent coexistence in the same person, but also by their coexistence in family groups. This has been revealed by practically all the reported genealogical statistics of epilepsy, but was specially stressed by Davenport and Weeks.[15] Calvert Stein[6] found mental deficiency in 1.8 per cent of the parents, siblings and offspring of his series of epileptic patients, and in only 0.1 per cent for the same relatives of his nonepileptic group.

As regards familial association of epilepsy with Little's disease, no statistical data seem to be available.

It is not to be supposed that all epilepsies are related to mental deficiency and Little's disease. The cases developing at adult ages or late in life on the basis of trauma of the head, tumor of the brain, neurosyphilis, cerebral arteriosclerosis and the like are, of course, not included in this consideration, but only cases in

TABLE 3.—*Age of Onset of Epilepsy in an Institutional Group*

Age at Onset	Number	Percentage of Ascertained Cases
Birth to 5 years	1,830	30.1
5 to 10 years	1,107	18.2
10 to 15 years	1,190	19.6
15 to 20 years	892	14.7
Over 20 years	1,056	17.4
Total ascertained cases	6,075	100.0
Age at onset unascertained	520	
Total admitted to Craig Colony to Jan. 1, 1926	6,595	

which the condition exists from birth or from an early age. The proportion of such cases in a large institutional group may be judged from the statistics of age of onset furnished in one of the reports of the Craig Colony[16] (table 3).

The relationship of epilepsy existing from birth or from an early age to mental deficiency and to Little's disease suggests a common factor of etiology for the three conditions, namely, trauma at birth.

In discussions of the etiology of epilepsy, mental deficiency and Little's disease the factor of trauma at birth has been mentioned often enough. We are led to bring the matter up for further discussion because the material has yielded new data, shedding additional light on this factor and on its manner of action.

TRAUMA AT BIRTH AND VULNERABILITY

In the majority of cases of epilepsy, mental deficiency and Little's disease no trauma at birth is reported. Often it is definitely stated that birth occurred at full term and was normal in every respect.

15. Davenport, C. B., and Weeks, D. F.: A First Study of Inheritance in Epilepsy, J. Nerv. & Ment. Dis. **38**:641 (Nov.) 1911.

16. Thirty-Second Annual Report of the Craig Colony, Sonyea, N. Y., 1926.

It is equally true that in the majority of cases of prolonged, difficult, instrumental labor resulting in the delivery of a cyanotic, partly asphyxiated child requiring measures of resuscitation, the child develops normally and without the supervention of epilepsy, mental deficiency or Little's disease.

It would seem that here were two factors: trauma at birth and vulnerability.

Trauma at birth cannot truly be said to be absent in any case, except perhaps in cases of prearranged delivery by cesarean section prior to the onset of labor. Nor can it be truly said that in any case the brain is wholly invulnerable. It must be judged merely that in the majority of births the traumatizing forces are not relatively severe enough or the vulnerability is not relatively pronounced enough for the labor to result in material injury to the cranial contents of the child.

The severity of the trauma at birth is dependent on the well known circumstances which determine more or less difficult labor: primiparity, especially in the fourth or fifth decade of life; breech or other abnormal presentations; early rupture of the amniotic sac; narrow pelvis or a pelvic obstruction of any kind; any condition necessitating the application of forceps, especially in the high forceps operation, and the like.

The degree of vulnerability, too, varies with many factors, and these merit more detailed analysis.

There is reason to believe that there is a hereditary vulnerability of the tissues of the central nervous system. The assumption of such a factor would be in harmony with the incontestable fact of a relatively high incidence of epilepsy and mental deficiency among the grandparents, parents, siblings, offspring and collateral relatives of epileptic persons as compared with nonepileptic controls. It is possibly the principal hereditary factor in epilepsy.

This assumption is, of course, not a new one. It was suggested years ago by Pierre Marie.[17] "Epilepsy is not the hereditary disease the almost fatal transmission of which to descendants has been the dread of past centuries. But nevertheless, does not one see, in some families, several persons with this malady? The fact is indisputable, and how is it to be interpreted aside from all idea of heredity? One might invoke a particular fragility of the tissues of the brain in certain families; that is possible, but very hypothetical, and we have no real proof of such fragility." More recently Calvert Stein[6] was led by observations made from his material to express a similar conjecture.

The assumption of a hereditary factor in vulnerability is in harmony with our findings among monozygotic and dizygotic twins: Both twins of the pair are affected, respectively, in 60.9 per cent and in 23.8 per cent of the cases of the two types of twins in our collection.

17. Marie, P.: Quelques considérations sur l'étiologie et sur le traitement de l'épilepsie, Presse méd. **36**:81 (Jan. 21) 1928.

It is not necessary to assume that all familial groupings of epilepsy and its borderland conditions are to be accounted for by a hereditary vulnerability. It should be borne in mind, on the one hand, that a group of siblings, for example, may be exposed to a common factor, such as a contracted pelvis in the mother or the preference of a family obstetrician for quick instrumental extraction; and, on the other hand, that other hereditary factors, indirectly increasing the hazard of epilepsy, may be involved, such as a tendency to twinning or toward premature labor.

Degree of vulnerability can be shown to be influenced to some extent by the factor of sex. This is indicated by the fetal mortality and mortality in childhood and by the incidence of mental deficiency and epilepsy in the two sexes.

It is well known that fetal mortality and mortality in childhood are consistently higher in the male than in the female sex. This is counterbalanced by the primary male/female sex ratio, which is very high. According to Auerbach,[18] the sex ratio of fetal mortality varies with the month of gestation as follows:

Month	Ratio
Second	4.52
Third	3.22
Fourth	2.29
Fifth	1.63
Sixth	1.16
Seventh	1.16

TABLE 4.—*Death Rates in Children per Thousand*

	Males					Females				
Country	0-1 Yr.	1-2 Yrs.	2-3 Yrs.	3-4 Yrs.	4-5 Yrs.	0-1 Yr.	1-2 Yrs.	2-3 Yrs.	3-4 Yrs.	4-5 Yrs.
Norway	81.4	18.4	8.6	6.3	5.2	66.8	16.8	9.0	6.2	4.9
United States	127.4	30.2	13.7	8.8	6.5	105.5	27.4	12.6	8.3	6.1
England	144.3	40.4	15.9	10.0	7.4	117.4	37.6	15.2	10.0	7.5
India	290.0	91.2	65.7	48.3	36.0	284.6	86.2	61.6	45.1	33.7

The sex ratio of stillbirths, without reference to the length of gestation, as given by Brodio, Davis, Heape, Quetelet, Rauber and others for countries of northwestern and central Europe and for the United States, varies between 1.246 and 1.445 or even higher.[19]

The so-called secondary sex ratio—the ratio among newly born infants—fluctuates between 1.04 and 1.06. A further equalization of the sexes in the population is accomplished by the relatively higher mortality in male infants, which is observed in all countries and under the most diverse conditions of infant welfare. This is shown in statistics of death rates in children per thousand for the years 1901 to 1910 in countries selected as representing good, bad and indifferent conditions of child hygiene[20] (table 4).

18. Auerbach, E.: Das wahre Geschlechtsverhältnis des Menschen, Arch. f. Rassen-u. Gesellsch.-Biol. **9**:10, 1912.

19. Crew, F. A. E.: The Human Sex-Ratio, Edinburgh M. J. **34**:122 (Aug.) 1927.

20. Woodbury, R. M.: Child and Infant Mortality, in Encyclopaedia of the Social Sciences, New York, The Macmillan Company, 1930, vol. 3, p. 385.

The greater frequency of mental deficiency in the male than in the female sex has been repeatedly noted. It is demonstrated in the most striking manner in twins of the opposite sex. In our own material pertaining to this matter, consisting of 81 pairs of twins of the opposite sex with mental deficiency, we find that both twins are affected in 34 instances, the boy alone in 31 instances and the girl alone in 16 instances. In other words, there is a relative excess of 30 per cent of cases of mental deficiency among the males as compared with females in our group of twins of the opposite sex.

This unequal distribution of mental deficiency seems to be attributable in part to a sex-linked genetic factor of intelligence, as is suggested not only by our material,[21] but also by an analysis of some recent European material.[22] However, for the most part, the unequal sex distribution, not only of mental deficiency but also of intelligence within normal limits, is apparently to be attributed rather to the relatively greater cerebral vulnerability of male fetuses, as we have shown in a recent communication dealing with this question.[21b]

The comparative incidence of epilepsy in the two sexes has never been exactly determined. Writers on the subject are not in complete agreement on this question. Institutional statistics are hardly acceptable, as they indicate rather the amount of provision for male and female epileptic patients that various states have made. The preponderance of the evidence in the literature is to the effect that the incidence of epilepsy is distinctly higher in males than in females.

The surest way of determining the sex distribution of epilepsy is by noting its occurrence in twins of opposite sex. Unfortunately, the amount of such material available is insufficient for final judgment. However, the indication is that there is a higher incidence in males.

In our material, among 45 pairs of twins of the opposite sex with epilepsy, both twins are epileptic in 7 instances, the male alone in 24 instances and the female alone in 14 instances, making a relative excess in males, as compared with females, amounting to 47.6 per cent.

A third factor influencing vulnerability is that of maturity at birth. It has been amply shown that premature birth, an underweight condition at birth or a combination of both determines a relatively high incidence of stillbirths and a relatively high mortality in infancy and early childhood.

For example, in the larger series of cases reported by Ylppö[23] the deaths occurred in the following percentages: by the end of the first day, 9.28 per cent; by the fifth day, 17.96 per cent; by the end of the first month, 30.84 per cent; by the end of the sixth month, 41.17 per cent. Further investigations (omitting 70 cases

21. (*a*) Rosanoff, A. J.: Sex-Linked Inheritance in Mental Deficiency, Am. J. Psychiat. **11**:289 (Sept.) 1931. (*b*) Rosanoff, A. J.; Handy, L. M.; Rosanoff, I. A., and Inman-Kane, C. V.: Sex Factors in Intelligence, to be published.

22. Luxenburger, H.: Endogener Schwachsinn und geschlechtsgebundener Erbgang, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:320, 1932.

23. Ylppö, A.: Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen, Ztschr. f. Kinderh. **24**:1, 1919.

which could no longer be traced, out of a total of 668 cases in the series) showed that by the end of the first year 50.33 per cent of the children had died; by the end of the second year, 52.67 per cent; by the end of the third year, 53.34 per cent, and by the end of the fourth year, 53.51 per cent.[24]

Among the surviving premature children there is a relatively high incidence of mental deficiency, Little's disease and epilepsy. This is indicated by both pathologic and clinical studies, such as those of Little,[25] Ylppö,[26] Schott,[27] Philipp Schwartz,[28] Capper,[29] Looft[30] and ourselves.[31]

The crucial evidence on this point is revealed by a comparison of dizygotic twins with siblings.

Obstetric experience shows consistently that premature birth, an underweight condition at birth or both occur much more frequently in connection with multiple than with single pregnancies. Hence, as one would expect, there is also a higher incidence of stillbirths and a higher mortality in infancy and early childhood among twins.

Among surviving twins there is a higher incidence of mental deficiency than among children born singly. Also, the reverse is true, i. e., that among the feebleminded there is a higher proportion of twins than among children of normal intelligence. We have observed and reported these relationships.[31] Similar observations have been reported by Looft,[32] who stated: "By statistical data I have shown that there are more twins among imbeciles and the feebleminded than among normal children. By an examination of 64 pairs of twins I have also shown that the number of imbecile and feebleminded subjects among them is greater than among children who are not twins."

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24. Ylppö counted as "premature" any infant who weighed 2,500 Gm. or less at birth, regardless of the length of gestation.

25. Little, W. J.: On the Influence of Abnormal Parturition, Difficult Labors, Premature Birth and Asphyxia Neonatorum, on the Mental and Physical Condition of the Child, Especially in Relation to Deformities, Tr. Obst. Soc. London **3**: 293, 1861-1862.

26. Ylppö, A.: Pathologisch-anatomische Studien bei Frühgeburten, Ztschr. f. Kinderh. **20**:212, 1919.

27. Schott: Die Bedeutung der Geburtsschädigungen für die Entstehung des Schwachsinns und der Epilepsie im Kindesalter, Arch. f. Gynäk. **113**:336, 1920.

28. Schwartz, P.: Erkrankungen des Zentralnervensystems nach traumatischer Geburtsschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **19**:263, 1924.

29. Capper, A.: The Fate and Development of the Immature and of the Premature Child, Am. J. Dis. Child **35**:262 (Feb.); 443 (March) 1928.

30. Looft, C.: Importance de la naissance avant terme dans l'étiologie des troubles de l'intelligence et du système nerveux chez l'enfant, Acta pædiat. **7**:15, 1928.

31. Rosanoff, A. J., and Inman-Kane, C. V.: Relation of Premature Birth and Under-Weight Condition at Birth to Mental Deficiency, Am. J. Psychiat. **13**: 829, (Jan.) 1934.

32. Looft, C.: L'évolution de l'intelligence des jumeaux, Acta pædiat. **12**:41, 1931.

As regards a comparison of dizygotic twins with siblings with reference to mental deficiency, it has already been statistically demonstrated by Humm [33] and by ourselves [31] that twins, as a group, are intellectually handicapped.

There is no reason for supposing that between dizygotic twins there is a closer genetic relationship than between siblings. So far as mental deficiency is of hereditary etiology, it should not be more common among the dizygotic twin brothers and sisters of epileptic persons than among their siblings. If found to be more common it could be attributed only to prenatal or intranatal factors, which are more often at work in multiple than in single pregnancies.

Among our 147 pairs of dizygotic twins, selected by reason of at least one of the pair having mental deficiency, we find that the other twin also had mental deficiency in 71 cases (48.3 per cent).

Among the 182 brothers and sisters (not twins) of his 50 subjects with mental deficiency, Humm found that only 24 (13.2 per cent) also had mental deficiency.

Turning again to epilepsy, its comparative incidence among twins and among subjects of single birth has not been determined. There is as yet no material available on which to base such statistics. It can readily be shown, however, that among the dizygotic twin brothers and sisters of epileptic persons there is a much higher incidence of epilepsy than among their single-born siblings.

Among the siblings of epileptic persons Humm [33] found 1.1 per cent of cases of epilepsy. In a larger mass of material Calvert Stein [6] found 4.1 per cent. His count, however, included not only established epilepsy, but "any kind of convulsion or fit that occurred one or more times in the life history of the relation of the patient."

In marked contrast, it is revealed by our material that among the dizygotic twin brothers and sisters of epileptic persons the incidence of epilepsy amounted to no less than 10.7 per cent.

The evidence seems conclusive that vulnerability is dependent in part on the degree of maturity at birth; that immaturity increases the hazard of trauma at birth and, with it, a corresponding hazard of epilepsy, and that these hazards exist in greater degree in multiple than in single pregnancy.

Probably a postnatal factor, too, should be mentioned as having a bearing on vulnerability of the brain, namely, the factor of age. It would seem that in infancy, childhood and adolescence the brain is more susceptible to injury than in adult life. We shall have occasion to refer to this point again.

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33. Humm, D. G.: Mental Disorders in Siblings, Am. J. Psychiat. **12**:239 (Sept.) 1932.

Before concluding the discussion of trauma at birth and vulnerability we wish to report one case of monozygotic female twins. In only one of the pair did epilepsy develop, in the first-born. She had borne most of the brunt of the labor and was, moreover, the lighter of the two in weight at birth. All else was equal, including, of course, their inheritance.

CASE 4.—*Monozygotic female twins, one affected.*

The B. twins, Edjuana and Juanita, were born in Los Angeles on Feb. 29, 1916. Edjuana was the first-born; delivery was difficult, and instruments were used, injuring the head and leaving a severe cut on one side of the face. Her weight was 3 pounds and 8 ounces (1,587 Gm.). She began to have convulsions at the age of 4 years; they occurred almost daily up to the age of 11 years. Since then they have been infrequent, but she has "violent spells" at the menstrual periods. She went to school at 7 years, but eventually had to be transferred to a "development school." She left school at 15 years when she was still doing work in the second grade. Juanita succeeded better, and the patient was always envious of her. Edjuana became troublesome in behavior; she would run away from home and be gone overnight and was restless, irritable and at times threatening. She also showed psychotic symptoms: She said "people had it in for her," told of imaginary attacks and was unstable emotionally, being at times depressed, at others hilarious and at others tempestuous and violent. Occasionally she would be seen standing in an awkward position for an hour at a time. She finally became so unmanageable that on May 23, 1932, she was admitted to the Pacific Colony, the institution for feebleminded persons at Spadra, Calif., and is still a patient there. It was judged that she not only was feebleminded to begin with, but also had suffered some mental deterioration. An intelligence test made prior to admission to the Pacific Colony revealed an intelligence quotient of 28. Physical examination on admission revealed a "body asymmetry; one side of the body is hollow." The Wassermann reaction was negative.

Juanita was born without difficulty and without the use of forceps. She weighed 4 pounds (1,814 Gm.). There was no trauma at birth. Physically the twins are identical as to color, form and texture of hair, color of eyes and skin, and there is a striking resemblance in features and build, except for the birth scar on Edjuana's head and face and her asymmetry. At the time of our investigation of the case (December, 1932), Juanita was in the ninth grade at school, had always done well in her studies and was of normal intelligence and in good health, both physically and mentally. She had never had a seizure.

POSTNATAL FACTORS

Among postnatal factors, too, trauma to the head occupies an important, perhaps a leading, position. We shall have occasion to refer to it again. At this time we shall submit abstracts from the clinical histories in 2 cases in which epilepsy was caused apparently by acute infections in childhood.

Epilepsy has often been attributed to acute infections in childhood, but mainly as a conjecture based on the one condition following the other in more or less close chronological sequence. Only cases observed

in monozygotic twins can furnish the controls necessary for a conclusive demonstration of acute infections as adequate causes of epilepsy.

In both of our cases only one of the pair had epilepsy. In the one twin it followed what seemed like an acute sporadic encephalitis, and in the other an attack of measles.

CASE 5.—*Monozygotic male twins, one affected.*

The F. twins, Edwin and Oliver, were born in Los Angeles on Jan. 8, 1924. Oliver was the first-born and was somewhat larger than Edwin. Aside from this they are much alike, being identical as to color of eyes, hair, skin and teeth. There was only one placenta. They both walked at 12 months, talked at 15 months and developed normally up to 3 years of age. At that time Edwin "had a severe case of indigestion with locked bowels for three days, which was followed by convulsions, occurring daily to as many as fifteen times, for a period of about a month." Since then he has not talked. Epileptic seizures have occurred about once a month and are usually mild. He has been taught to take care of himself in the toilet, but is not otherwise teachable.

Oliver is in school, doing average work. A mental test made in September, 1930, revealed an intelligence quotient of 99. He is in good health and free from any manifestations of epilepsy.

CASE 6.—*Monozygotic female twins, one affected.*

The T. twins, Grace Olive and May Alice, were born in Chicago on April 18, 1890. Height, color of eyes, hair and skin were identical; in features the resemblance was so close that they were often mistaken for each other when seen apart; when seen together they could be distinguished, as Grace was stouter. Grace began to have convulsions in childhood, during an attack of measles. These continued and led to mental deterioration and the development of marked irritability, especially during menstrual periods. She reached only the sixth grade in school. Following seizures she would often become violent, and on March 5, 1920, she was taken to the Kankakee State Hospital (Ill.). At the time of our investigation of the case (July, 1932) she was still a patient there; seizures were then occurring at the rate of about fifteen a month.

May finished grammar school and has since worked as a seamstress. As a child she was subject to severe headaches "over the whole head," but has outgrown them. She is somewhat "nervous" and "fidgety," but otherwise normal and not in any way incapacitated; she has never had convulsions and has never required institutional care.

THE FACTOR OF AGE

That epilepsy is a disease mainly of the first two decades of life has been noted by all students of the subject; but it has never been explained. Thus, it appears from the statistics from Craig Colony that the onset of epilepsy occurred before the age of 20 years in 82.6 per cent of all ascertained cases, and after that age in but 17.4 per cent. It should be specially noted that this age distribution is true not only of epilepsy in general but also of cases of known traumatic etiology. In other words, it appears that a trauma to the head at birth or in childhood is much more apt to result in epilepsy than an injury sustained at an adult age.

As a matter of fact, trauma to the head in adults rarely results in epilepsy. Thus, Sargent [34] reported that only 4.5 per cent of 18,000 soldiers with craniocerebral wounds and defects of the skull, sustained in the World War, showed epilepsy. Reichmann [35] reported a study of 603 cases of fracture of the skull occurring in time of peace and concluded: "True traumatic epilepsy is an extraordinarily rare disease in adults. Such cases occur among skull fractures at the highest in 0.5 per cent. Their number would undoubtedly be materially still less if all head injuries were taken into consideration."

If the theory is correct, according to which epilepsy is a decerebration syndrome, the question arising in this connection should be formulated somewhat as follows: Why is a decerebrating lesion more readily produced by a trauma to the head at birth or at an early age than at an adult age?

It seems to us that the fundamental point involved here consists in the well known fact of the greater ability possessed by brain tissue to withstand compression than to oppose extension. For example, in the process of molding the head during birth the decerebrating lesion is produced, in all probability, not so much by the generally incriminated compressing forces which are applied along the transverse diameters as by the forces along the vertical axis to which the brain substance is subjected and which consist in compensatory extension. It is obvious that, save in cases of massive hemorrhage, the pressure which is exerted on the brain during birth has the effect not of reducing its volume but merely of altering its shape by compressing it in one direction while extending it in another.

It is equally obvious that in infancy, prior to the closure of the fontanels and ossification of the sutures, a fall on the head, a kick by a horse, a carriage wheel running over the head, and the like, similarly has the effect of applying not only compression but also extension to the brain substance.

Even in later childhood or in adolescence, before the skull has attained its full growth and rigidity, it has undoubtedly a great enough flexibility so that blows can still have the effect of marked extension as well as of compression.

At adult ages, when the skull has become fairly rigid, a decerebrating lesion can hardly be produced otherwise than by direct extensive bruising and destruction of the substance of the brain such as may result from

34. Sargent, P.: Some Observations on Epilepsy, Brain **54**:312, 1921.

35. Reichmann, V.: Ueber Entstehung und Häufigkeit epileptischer Krämpfe nach Schädelbrüchen an der Hand von 603 Fällen, Deutsche Ztschr. f. Nervenh. **96**:260, 1927.

fractures of the vault by direct violence. Hence, in adults, fractures of the base hardly ever produce epilepsy, as Reichmann,[35] among others, has pointed out.

Epileptic seizures, like other manifestations of decerebration, are produced in middle life or later by mechanisms which are quite unlike those operating in cases of trauma. In supratentorial tumors the inhibition of cerebral function is produced, no doubt, by widespread compression of the cortex against the bones of the skull: in dementia paralytica and in cerebral arteriosclerosis, by widespread cortical atrophy and destruction.

Finally, it should be noted, as having a bearing on the decerebration theory of epilepsy, that phenomena of decerebration, including epileptiform seizures, can be produced without a lesion of the brain, but by the effect on the brain of toxic factors (alcohol and absinth), autotoxic factors (eclampsia, uremia and hyperinsulinism) and circulatory factors (aortic lesion, heart block, etc.).

TABLE 5.—*Relation of Epilepsy to Order of Birth (Green)*

Order of Birth	Number of Children	Number Epileptic	Percentage Epileptic
First	1,000	240	24.0
Second to fifth	3,310	599	18.1
Sixth or later	1,772	161	9.1

ORDER OF BIRTH IN RELATION TO EPILEPSY

It has been pointed out, particularly by Karl Pearson,[36] that mental deficiency, criminality, psychoses and some other handicapping conditions occur relatively more often among the first-born than among the later-born. The same seems to be true of epilepsy.

Thus, from statistics on the order of birth furnished by Shanahan,[37] based on data pertaining to patients admitted to the Craig Colony, it appears that among a total number of 10,039 children in families of from 2 to 20 children, with at least 1 epileptic child in each family, there were 1,709 first-born and 8,330 later-born children. Of the first-born children 402, or 23.5 per cent, were epileptic; of the later-born, 1,307, or 15.7 per cent, were epileptic.

Similar statistics have been furnished by Green,[38] from whose data interesting figures have been derived.

36. Pearson, K.: The Handicapping of the First-Born, London, Galton Laboratory Publications, 1914.

37. Shanahan, W. T.: Convulsions in Infancy and Their Relationship, if Any, to a Subsequent Epilepsy, Psychiatric Quart. **2**:27 (Jan.) 1928.

38. Green, W.: Order of Birth as a Factor in Epilepsy, J. Michigan M. Soc. **27**:525 (Aug.) 1928.

The usual and obvious interpretation of such figures is to the effect that they discount heredity as an adequate or essential factor in the etiology of epilepsy. They point to trauma at birth as a factor, such a factor coming into play more often in cases of primiparas than in those of multiparas.

PATHOGENESIS OF TRAUMATIC EPILEPSY

It is not difficult to understand infantile cerebral palsies, extrapyramidal syndromes, mental deficiency and mental deterioration as phenomena of decerebration which may result from trauma to the head. The case is different with regard to epilepsy. Perhaps the most puzzling feature is the periodicity of some of its manifestations.

Possibly for some cases, especially those of jacksonian type with readily localizable lesions, the theory advanced by Penfield,[39] Foerster [40] and others holds the correct explanation, namely, that cicatricial traction, by producing a spreading reflex vasomotor spasm, starts the seizures; and it may be that this theory has some bearing on other types as well. The available facts indicate, however, that an unqualified generalization would hardly be permissible, and that even in the traumatic group alone cases must differ widely as to details of pathogenesis.

Sometimes one or more seizures occur immediately or shortly after trauma at birth or postnatal trauma. With recovery from the immediate effects of the trauma, in many cases the seizures subside never to return. In other cases, after an interval of weeks, months or years, the seizures recur and become established over a period of years or permanently.

In still other cases the seizures make their first appearance not immediately after the trauma, but after an interval of weeks, months or years. This has been so often observed that it must be regarded as incontestable. We select, at random: the reports of Bychowski [41] pertaining to cases resulting from trauma received during the World War, in which the first seizures occurred at intervals varying from three months to two years after the trauma; those of Reichmann[35] pertaining to cases in time of peace, in which the first seizures occurred immediately following a trauma or after intervals varying up to three years; those of Foerster and Penfield,[40b] including cases of trauma at birth as well as postnatal trauma, in which the time that elapsed between the trauma and the first seizure was from two to nine years, and those of Fincher and Dowman,[42] pertaining mainly to cases of jacksonian character, with intervals between the trauma and the first seizure varying up to fourteen years, and, in one case of trauma at birth held by the authors as open to question—amounting to nineteen years.

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39. Penfield, W.: The Mechanism of Cicatricial Contraction in the Brain, Brain **50**:449 (Oct.) 1927.

40. (*a*) Foerster, O., and Penfield, W.: Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930; (*b*) The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99 (July) 1930.

41. Bychowski, Z.: Zur Statistik der traumatischen Epilepsie im Kriege, Neurol. Centralbl. **38**:423 (July 1) 1919.

42. Fincher, E. F., and Dowman, C. E.: Epileptiform Seizures of Jacksonian Character, J. A. M. A. **97**:1375 (Nov. 7) 1931.

No doubt the many cases of a long interval between trauma and first seizure have been a cause of underestimating the importance of trauma in the etiology of epilepsy. This must be especially true with reference to cases of trauma at birth; for in such cases the fact of the trauma is often entirely overlooked or lightly disposed of by those in attendance and either remains unknown or is forgotten by the parents or the patient. Thus in many cases the clinical history taken in later years yields no clue to the etiology, but leads to classification in the "idiopathic" group.

In the majority of traumatic cases one is dealing apparently not with immediate effects of trauma, but with a chronic and progressive pathologic process in the tissues, which is initiated by the trauma and which, in its turn, eventually produces the epilepsy.

The fact of the progressive nature of the posttraumatic lesion in many cases is borne out, not only by the delay in the occurrence of the first seizure, but also by both clinical and pathologic data. On the clinical side the evidence consists in cases characterized by steady increase in the severity and frequency of the seizures and by a more or less rapid mental deterioration. On the pathologic side the evidence consists in the well known changes which are obviously of long development—dilatation and distortion of the ventricles of the brain, cysts, atrophies, adhesions, scleroses, almost tumor-like scars, overgrowths of neuroglia and the like.

Here, too, generalizations are not permissible, as the subject bristles with complexity. A progressive course is not observed in all cases. In many cases the course is merely chronic, without aggravation of the seizures and without any mental deterioration. In some other cases the course seems to be self-limited, characterized by gradual improvement and perhaps terminating in spontaneous recovery—this especially in children who are said to have "outgrown" the fits.

There is strong evidence that the epileptic syndrome in traumatic cases is determined not by the severity or extent of the original injury to the brain, but, it must be inferred, by its localization or by the inflammatory reaction with progressive change in the tissue which follows it, or by both.

Often a trauma at birth sufficiently severe to produce completely crippling Little's disease or a low grade of imbecility, or a combination of both, leaves the subject entirely free from epileptic seizures of any kind. On the other hand, many cases of epilepsy which can be attributed only to trauma at birth are free not only from mental deficiency and any traces of cerebral palsy, but also from all other neurologic and roentgenologic evidence of a lesion of the brain. In such cases, obviously, the decerebrating lesion which the theory assumes to exist must be a slight one and localized in a "silent" region.

However this may be, the possibility must be stressed of epilepsy resulting from a slight trauma to the head. This position alone affords

an explanation for the greater frequency of epilepsy among the first-born than among later-born children already referred to.

This position, moreover, is in harmony with the observations reported years ago by Sharpe and Maclaire,[43] which showed how much more often evidence of intracranial hemorrhage in the new-born is discovered with the aid of routine spinal puncture than by clinical observation alone. In cases of twins in which only one of the pair is epileptic it is much more common for the first-born than for the second-born twin to be the one thus affected. This is true of monozygotic as well as of dizygotic twins. Case 4, in which the first-born twin was known to have sustained a trauma at birth while the second one escaped it, illustrates this point. We cite here another case, in which epilepsy developed in the first-born twin alone, at the age of 8 years, although at the time of birth no evidence was noted of his having sustained a trauma to the head.

Fig. 1.—The C. twins, Harold and Merrill.

CASE 7.—*Monozygotic male twins, one affected.*

The C. twins, Harold and Merrill, were born in Los Angeles on May 25, 1924. A paternal uncle had had nocturnal epileptic attacks at the age of 4 years; these occurred at the rate of about one a month until he was 7, when they ceased; he has been free from them since. The family history was otherwise negative for epilepsy. There were four older children, all living and well.

The birth of the twins was due to occur on June 26, but labor set in on May 24, instead, and lasted about twenty-one hours, delivery occurring on the morning of May 25. Both were delivered by breech presentation. Harold was the first-born; he showed slight molding of the head, was 39.5 cm. long and weighed 1,819.4 Gm. Merrill was a little smaller, being 38.5 cm. long and weighing 1,632.8 Gm. There was only one placenta. In color of eyes, hair, skin and features the twins are identical. A picture taken of them in June, 1933, is reproduced in figure 1. No evidence of trauma to the head was observed at birth, other than the already

43. Sharpe, W.: Intracranial Hemorrhage in the New-Born, J. A. M. A. **81:** 620 (Aug. 25) 1923. Sharpe, W., and Maclaire, A. S.: Further Observations of Intracranial Hemorrhage in the New-Born, Am. J. Obst. & Gynec. **8:**172 (Aug.) 1924.

mentioned slight molding of the head in Harold. They were kept in an incubator in the hospital for several months, Merrill remaining for some weeks after Harold was discharged, as it took him longer to attain the minimum weight of 5 pounds (2,268 Gm.) required by the hospital for discharge. At 8 months they had chickenpox and made uneventful recoveries. At 14 months they were treated for rickets and general malnutrition, but made good progress and thereafter developed normally. They had whooping cough at 3 years, measles at 3½ and mumps at 6, with full recovery from each. In the spring, 1932, a Stanford-Binet intelligence test was made which revealed, in Harold's case, an intelligence quotient of 90 and in Merrill's case, 93.

In August, 1932, a member of the family attended a wedding and brought home some of the cake. The next morning Harold ate a piece and went out to play. Otherwise there was no variation from his daily routine. At 10 a. m. he became very pale and started to fall. His sister, who had noticed him, caught him. "He stiffened out, his eyes rolled and became glazed, and the right side of the face drew up. He twitched and trembled, but finally relaxed; it was a few minutes before he could speak." He had another attack a week later, and from then on attacks recurred with increasing frequency until he was having them almost daily and on some days two or three times. In October, 1932, he was hospitalized for observation for a few days. He had some convulsions there, but the neurologic findings were otherwise negative. The Wassermann and Kahn reactions were negative. Tests of the spinal fluid showed negative results, except for a cell count of 30 per cubic millimeter, 50 per cent polymorphonuclears and 50 per cent lymphocytes. He was treated with a ketogenic diet and phenobarbital, but the seizures continued, though less frequently. In January, 1933, he was taken out of school. Merrill remained in school, as he was and still is (May, 1933), free from seizures. In May, 1933, a Stanford-Binet test was made, which revealed in Merrill's case an intelligence quotient of 88, but in Harold's case one of only 73, indicating mental deterioration.

The facts that epilepsy can develop as a result of even slight trauma to the head, and not immediately, but after an interval of months or years, that it often runs a progressive course and that it is in many cases associated with mental deterioration, which is likewise progressive, suggest that the expressions "fragility," used by Marie, and "vulnerability," used by us, to designate the proneness of some persons toward that disease and certain related conditions are perhaps not the words of first choice for specifying the nature of that proneness.

The proneness may consist rather in a tendency on the part of the central nervous system toward a special type of reaction of the vascular, connective and glial tissue to trauma. At any rate, in the following remarkable case of monozygotic twins epilepsy developed in one of the pair following a postnatal trauma, while the other remained free from epilepsy but later had a meningioma in the spinal canal following an injury to the back.

CASE 8.—*Monozygotic female twins, both affected, but in a manner qualitatively dissimilar.*

The M. twins, Gertrude and Constance, were born in Ontario, Canada, on Sept. 5, 1879. The mother had given birth to five children (including another pair

of twins) before, and had three children after these twins were born. Labor was at full term and normal in every respect. There was only one placenta. The twins were identical as to color and texture of hair and skin, color of eyes and features. A picture taken of them at the age of 3 years is reproduced in figure 2. They developed equally and went to school together, up to the age of 15 years, when Gertrude hurt herself in an accident. She was in a hammock, swinging hard, when it gave way and she was thrown "flat on her back." She was not rendered unconscious and showed no immediate ill effects, but a week later had an obscure illness with delirium and nausea, which lasted about a week. Although she seemed to recover, she was frail afterward; she was able, however, to continue at school with Constance up to the time of entrance to college, at about 18 years. A few months after the first accident she had another. She was at the top of a ladder, on the level of a second story window, when some children pulled the

Fig. 2.—The M. twins, Gertrude and Constance.

bottom of the ladder and she fell. It is not known whether she was stunned or not, but if so it was only for a few seconds as she was able to walk to the house without help. "She was sick, badly shaken," but was not laid up. At the age of 17 years, seizures began. They were at first petit mal for several years, but then assumed the grand mal form. At about the age of 25 years she began to show "increasing mental dulness" and eventually was placed in a private sanatorium where she remained for seventeen years. From there she was transferred to the Ontario Hospital at Whitby, Canada, and at the time of this record (September, 1933) was still a patient there. In the past two years, under heavy medication with phenobarbital, she has had but few seizures. As regards her mental condition "she still has a well preserved personality, but very narrow interests; she is occasionally irritable, and has a marked shallow religious trend."

Constance has never had epilepsy or mental trouble. She continued her education to within a year of graduation from college, when she left to marry. She was always well until 1916, when she fell from a horse, striking the left hip. This occurred in a country place, and the exact nature of her injury was not determined

at the time; about fourteen years later a roentgenogram showed evidence of an old fracture of the pelvis. For four or five weeks after the accident she suffered pain of an encircling character about the lower thoracic and upper abdominal regions. This was then replaced by persistent pain in the left hip from which she suffered for fourteen years. In 1930, the pain spread to the right hip and from that time on the condition grew progressively worse until there developed paraplegia, the "riding breeches" type of anesthesia, impaired control of the sphincters and other evidences of a lesion of the cord. On April 10, 1933, she was operated on, and a meningioma, about 2 cm. in diameter, was removed. It was located on the right side, anterolaterally, at the level of the twelfth dorsal vertebra. The patient began to improve almost immediately; motion, sensation and sphincter control were quickly restored, and at the time of our observation (September, 1933) she was walking and otherwise functioning almost normally.

THE BORDERLAND OF EPILEPSY

The relationship existing between epilepsy and mental deficiency and Little's disease has already been discussed. The borderland of epilepsy is replete with some other conditions as well, suggesting further important relationships.

Epilepsy is frequently complicated with psychotic disease in degrees which necessitate commitment to a hospital for mental diseases. Thus, according to statistics furnished in the report of the New York State Department of Mental Hygiene for the year ended June 30, 1932,[13] the census of patients as of that date in the various state hospitals shows that among a total number of 56,804 patients, 1,247 (2.2 per cent) had epileptic psychoses.

Practically all statistics show that there is also a familial relationship between epilepsy and psychotic disease, for such disease is found at least twice as often among the near relatives of epileptic patients as among those of normal controls. (Among the most recently compiled statistics yielding such a finding are those of Calvert Stein.[6])

Here epilepsy resembles mental deficiency, for the latter, too, is frequently complicated with psychotic disease. According to the New York report already referred to there were 2,093 cases of "psychoses with mental deficiency"—3.7 per cent of all cases in the state hospitals.

In cases of epilepsy with psychosis there is not always a close correspondence in the respective severities of the epileptic and the psychotic manifestations. In any large hospital for mental diseases one is sure to find cases in which seizures occur but two or three times a year or even less often and in which there are persistent and troublesome psychotic manifestations associated with progressive mental deterioration.

In the history in such cases it appears sometimes that the onset of the mental disorder preceded the seizures. Occasionally it happens even that epileptic seizures appear for the first time after a period of weeks, months, or even years following a patient's commitment to a hospital for mental diseases.

The official diagnosis in institutional cases in which there is a coexistence of epileptic seizures and psychotic symptoms is not subject to any uniform policy: it may be "epileptic psychosis" or "dementia praecox," depending on the sequence of events in the given case, on the relative prominence of the epileptic and psychotic features in the clinical picture or on the subjective judgment of the physician in charge of the matter.

A similar situation exists in connection with mental deficiency. The official diagnosis in some cases is "psychosis with mental deficiency," while in others it is "dementia praecox" or a "paranoic condition," with "subnormal intellectual make-up." Thus, according to the statistics for the New York state hospitals,[13] among the first admissions for the year ended June 30, 1932, there was 2,640 cases of dementia praecox with an ascertained intellectual make-up. In 447 of these the intellectual make-up was rated as subnormal in degrees amounting to imbecility, moronism or borderline intelligence, i. e., not less than 16.9 per cent.

In this connection it should be recalled again that psychotic disease, like mental deficiency and epilepsy, has been shown to occur with greater frequency among the first-born than among the later-born.[36] Another fact that may be of some relevancy here is that so-called dementia praecox, again like mental deficiency and epilepsy, is more common in the male than in the female sex: among the first admissions to the New York state hospitals during the year ended June 30, 1932, there were 2,755 patients with dementia praecox, of whom 1,486 were males and 1,269 were females—showing a relative excess among males amounting to 17.1 per cent.[13]

These considerations, together with the case of monozygotic twins, already cited (case 3), in which one had epilepsy and the other "dementia praecox," suggest that some cases of chronic deteriorating psychosis are but another clinical type of decerebration, based on an etiology similar to that in many cases of epilepsy, mental deficiency and Little's disease. Each of these conditions may exist in various degrees of severity, either alone or in every possible combination with one or more of the others. Presumably, in cases traceable to trauma at birth the particular clinical type of the decerebration is determined by the localization, severity and extent of the injury to the brain and of the changes in the tissue which follow the injury through the years of infancy, childhood and adolescence.

There seems to be also a relationship between epilepsy and some cases of problems in behavior and criminality. The impulsive, poorly controlled, at times tempestuous and violent behavior of epileptic persons has often been noted, not only in patients under treatment in hospitals for mental diseases, but also in those cared for in institutions for "sane" epileptic persons and in those at large.

There is a much higher incidence of epilepsy among inmates of reformatories and prisons than in the unselected population—2.4 per cent according to Sheldon and Eleanor Glueck,[44] which is at least five times

44. Glueck, S. S. and E. T.: Five Hundred Criminal Careers, New York, Alfred A. Knopf, 1930.

as high as in the unselected population. The significance of this finding is perhaps increased in the light of the further—and very common—finding of an abnormally high incidence of psychotic disease and subnormal intelligence among inmates of reformatories and prisons: according to Sheldon and Eleanor Glueck, 3.4 and 42.9 per cent, respectively. The latter figure includes: "feeblemindedness" (intelligence quotient from 50 to 70), 20.6 per cent, and "borderline deficiency" (intelligence quotient from 70 to 80), 22.3 per cent.

Recent studies of criminality in twins, particularly those which have been reported by Lange [45] and by ourselves,[46] have brought to light cases in which one of the pair of monozygotic twins, apparently by reason of a trauma at birth or a postnatal trauma, showed persistent criminal behavior, while the uninjured twin remained free from any criminal tendency. Once more we refer to Karl Pearson's finding of a greater incidence of criminality among the first-born than among the later-born.[36]

One cannot explore the borderland of epilepsy without being almost immediately confronted with the issue of jacksonian epilepsy. In cases in which the question of surgical intervention is raised it is perhaps of practical advantage to continue to distinguish jacksonian from "genuine" epilepsy. As all know, however, a sharp line of demarcation cannot be drawn between the two types of fits. In any large collection of clinical material every degree of transition from the one type to the other can be observed. Moreover, manifestations of the one type often merge into those of the other type in course of time in the same case. It would seem merely that the jacksonian type of fit is dependent on a more sharply circumscribed, and therefore more readily localizable, decerebrating lesion.

Among the milder conditions to be found in the borderland of epilepsy should be mentioned left-handedness. Lombroso and one or two other Italian observers were the first to note that left-handedness occurred with relatively greater frequency among epileptic persons than in the unselected population. This finding has since been repeatedly confirmed by Redlich,[47] Steiner [48] and others. These observers reported the incidence of left-handedness among epileptic persons as amounting

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45. Lange, J.: Crime and Destiny, translated by C. Haldane, New York, Albert & Charles Boni, Inc., 1930.

46. Rosanoff, A. J.; Handy, L. M., and Rosanoff, I. A.: Criminality and Delinquency in Twins, J. Crim. Law & Criminol. **24**:923 (Jan.-Feb.) 1934.

47. Redlich, E.: Epilepsie und Linkshändigkeit, Arch. f. Psychiat. **44**:59, 1908; Nochmals Epilepsie und Linkshändigkeit, Epilepsia **3**:250, 1912.

48. Steiner, G.: Ueber die Beziehung der Epilepsie zur Linkshändigkeit, Monatschr. f. Psychiat. u. Neurol. **30**:119, 1911; Ueber die familiäre Anlage zur Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **23**:315, 1914

to from 10 to 18 per cent, while in the normal population the rate is, at the most, 5 per cent.

In the families of epileptic persons, too, an abnormally high incidence of left-handedness is to be found, according to these authors. Redlich found that 48.5 per cent of the epileptic persons in the group investigated by him had one or more near relatives who were left-handed. A similar investigation, made by Steiner, yielded an even higher figure—89 per cent. The finding is the same regardless of whether the epileptic patients whose families are studied were themselves right or left handed. Steiner reported, further, that among the relatives of 294 left-handed subjects he found an incidence of epilepsy amounting to 4.1 per cent, while in 273 pure right-handed families from approximately the same environment (soldier material) not a case of epilepsy was found.

Various hypotheses have been advanced in explanation of these findings. Redlich's suggestion seems to be in closest harmony with other facts pertaining to epilepsy. According to him, in left-handed epileptic persons, or in most of them, a trauma affecting mainly or solely the left cerebral hemisphere is the cause of both the epilepsy and the left-handedness.

In other words, some cases of left-handedness seem to represent but another clinical manifestation of partial decerebration. Its familial occurrence and relationship to epilepsy and also its high incidence among twins suggest its dependence, to some extent at least, on the factor of vulnerability, already discussed.

We know that our enumeration has not exhausted the list of conditions which properly belong to the borderland of epilepsy. It would be interesting to investigate from that standpoint such conditions found among school children as stammering and other disorders of speech, and the cases of "nonreaders" and poor spellers (in spite of normal or superior intelligence), all of which seem to be more or less closely associated with left-handedness, are more common in the male than in the female sex and have a higher incidence among feebleminded and epileptic than among normal children. One would indeed anticipate *a priori* that a cerebral trauma at birth would in some cases involve portions of the mechanism of speech and give rise to the suggested disturbances. Thus, some of these cases, too, may eventually be shown to be but special clinical types of partial decerebration.

SUMMARY: THEORY OF EPILEPSY AND ALLIED CONDITIONS

A general survey of 107 cases of epilepsy in twins is presented. As regards the type of twins these cases are classified as follows: monozygotic, 23; same sex, dizygotic, 39; opposite sex, dizygotic, 45.

The material was selected on the basis of at least one of the twins having epilepsy. The distribution of epilepsy and other neuropsychia-

tric conditions found among the other twins of the pairs is as follows: (1) in monozygotic twins, epilepsy, 12; deteriorating psychosis and tumor of the spinal cord, 1 each; normal, 9 (39.1 per cent); (2) in dizygotic twins, epilepsy, 9; mental deficiency, 6; mental deficiency with psychosis, mental deficiency with behavior difficulty, deteriorating psychosis, behavior difficulty and dementia paralytica, 1 each; normal, 64 (76.2 per cent).

Hereditary factors undoubtedly exist in the etiology of epilepsy, as is indicated by the comparison of monozygotic and dizygotic twins.

The hereditary factors are often, in themselves, inadequate for the production of epilepsy, as is indicated by the large percentage of cases among monozygotic twins in which only one of the pair is affected.

The hereditary factors are not invariably present—therefore not essential—in the etiology of epilepsy, as is indicated by the high percentage of cases among dizygotic twins in which both of the pair are affected. This point is revealed most clearly by a comparison of dizygotic twin brothers and twin sisters with siblings of epileptic subjects; the percentages of those having epilepsy in the two groups, respectively, have been found to be 10.7 and from 1.1 to 4.1.

Identicalness of manifestations in both twins of a pair is the exception rather than the rule, even in cases of monozygotic twins, as far as epilepsy is concerned. The dissimilarities in cases of both twins involved are quantitative (i.e., as to the age of onset, frequency and severity of seizures, remissions, mental complications and outcome) and qualitative (i.e., the other twin has no epilepsy, but some other neuropsychiatric condition, such as mental deficiency or psychotic disease). The dissimilarities are greater and more frequent in dizygotic than in monozygotic twins.

Epilepsy, especially that existing from birth or from an early age, is closely related by both individual and familial association to certain cases of mental deficiency and Little's disease. The borderland of epilepsy is moreover replete with other conditions, particularly psychotic disease, behavior problems, jacksonian fits, left-handedness and possibly certain conditions often seen among school children, namely, stammering, other disorders of speech and cases of "nonreaders" and constitutionally poor spellers.

Evidence has accumulated in the past fifteen or twenty years to the effect that epilepsy, traditionally considered a neurosis, functional in nature and "idiopathic" in etiology, is rather a decerebration syndrome, definitely organic.[49]

Its relationship to other decerebration syndromes, such as mental deficiency, Little's disease and the other conditions already mentioned, suggests a common factor of etiology, namely, trauma at birth.

49. Of course, this has no reference to the epileptiform seizures which are often seen in cases of hysteria or malingering.

In most cases of epilepsy, even with onset in childhood, no trauma at birth appears in the history. Also most cases of known trauma at birth do not lead to epilepsy. The same is true of other clinical types of decerebration.

There seem to be two factors involved: trauma at birth and vulnerability.

Trauma at birth cannot be said to be wholly absent in any case; nor can it be said that in any case the brain is wholly invulnerable. It must be judged merely that in the majority of childbirths the traumatizing forces are not relatively severe enough or the vulnerability is not relatively pronounced enough for the labor to result in material injury to the cranial contents of the child.

The severity of trauma at birth is determined by conditions causing dystocia: primiparity, premature rupture of the membranes, abnormal presentations and contracted pelvis.

The degree of vulnerability also varies according to certain conditions, among which may be mentioned: a hereditary factor; a sex factor (male fetuses and infants being more vulnerable); premature birth or an underweight condition at birth, and the handicapping conditions of multiple pregnancy.

It has been shown statistically that epilepsy, mental deficiency and some other clinical types of decerebration occur with relatively greater frequency among the first-born than among the later-born—a fact which also points to trauma at birth as an important factor in the etiology of these conditions.

In connection with postnatal trauma, age seems to be an important factor in the etiology of epilepsy. Whereas trauma to the head sustained in infancy, childhood or adolescence frequently causes epilepsy, in later life it does so in but a very small percentage of cases.

The answer to the question: Why is a decerebrating lesion more readily produced by trauma to the head at birth or at an early age than at an adult age? seems to be contained in the relatively greater flexibility of the skull in young subjects.

It may be surmised that decerebrating lesions are produced not by the compressing forces of a trauma, but rather by the compensatory extension which takes place at right angles to the compressing force in view of the well known greater ability of the tissues of the brain to withstand compression than extension.

In many cases the seizures make their first appearance not immediately after the natal or postnatal trauma, but after an interval of weeks, months or years. It is obvious that one deals in such cases, not with the immediate effects of trauma, but with a chronic and progressive pathologic process in the tissue, which is initiated by the trauma and which, in its turn, eventually produces the epilepsy.

The assumption of the progressive nature of the posttraumatic lesion in many cases is borne out clinically by a steady increase in the frequency and severity of the seizures and by increasing mental deterioration, and pathologically by the chronic types of organic change observed, such as dilatation of the ventricles, cysts, atrophies, adhesions, scleroses, almost tumor-like scars and overgrowths of neuroglia.

Apparently the epileptic syndrome in traumatic cases is determined not by the severity or extent of the original injury to the brain but, it must be inferred, by its localization or by the inflammatory reaction with progressive tissue change which follows it, or by both.

At any rate, the possibility must be stressed of epilepsy resulting from a *slight* trauma to the head.

Chronic and deteriorating psychotic disease is frequently associated with epilepsy both in individual cases and in familial groups. In individual cases there is not necessarily a correspondence in severity between the epileptic and the psychotic manifestations. These facts, together with evidence yielded by some cases among twins, indicate that some chronic and deteriorating psychoses which are usually counted as dementia praecox in the statistics of state hospitals are really but a special clinical type of decerebration, based on an etiology similar in many cases to that of epilepsy, mental deficiency and Little's disease.

While we have stressed the factor of trauma to the head, natal and postnatal, as the most important cause of the decerebration underlying epilepsy and related conditions, we have said little concerning other factors for the reason that our material contains very few cases exemplifying a nontraumatic etiology.

However, the occurrence of epileptic syndromes in connection with nontraumatic conditions is not inconsistent with the decerebration theory of epilepsy. Undoubtedly decerebrating effects can be produced by a tumor of the brain, neurosyphilis and cerebral arteriosclerosis; or, even in the absence of brain lesion, by toxic (alcohol, absinth), autotoxic (eclampsia, uremia, hyperinsulinism), infectious (scarlet fever, measles) or circulatory (aortic lesion, heart block) factors.

ENCEPHALOGRAPHIC STUDIES IN MANIC-DEPRESSIVE PSYCHOSIS

REPORT OF THIRTY-EIGHT CASES

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With controversy rampant among the various schools of psychiatric thought concerning the possible etiologic factors in the psychoses, from the point of view of functional versus organic change, we have endeavored to demonstrate, through the medium of encephalography, the organic, structural deviations from the normal in the brains of psychotic persons. In a previous communication,[1] in which encephalographic studies of sixty schizophrenic patients were reported, the conclusions indicated that definite organic changes existed, as manifested by the failure of any encephalographic study to reveal a normal cerebral pattern.

Ebaugh, Dixon, Kiene and Allen, Ginzberg and Hermann and Herrnheiser showed marked changes in cerebral architecture in their encephalographic studies in dementia paralytica. Jacobi and Winkler indicated structural abnormalities in encephalograms of schizophrenic patients.

Thus far, no series of cases of manic-depressive psychosis, studied from the encephalographic standpoint, has come to our attention in the literature.

MATERIAL AND METHOD

The present series of encephalographic studies comprises thirty-eight cases of manic-depressive psychosis in various stages of the manic-depressive cycle. Of the patients, thirty-six were women and two were men. The ages varied from 21 to 54 years. The following data were included in the study of each patient: age, sex, married or single, race, duration of psychosis since first symptom, number of attacks, nature of reaction, remissions, condition during remission, hallucinations and delusions, former illnesses and family history. Serologic tests of both the blood and the spinal fluid gave negative results in every case.

From the Norristown State Hospital, Norristown, Pa.

1. Encephalographic Studies in Schizophrenia (Dementia Praecox), Am. J. Psychiat. **12**:801 (Jan.) 1933. This paper was presented at the Eighty-Eighth Annual Meeting of the American Psychiatric Association, Philadelphia, May 31, 1932.

The same encephalographic technic that was used in the earlier series of sixty schizophrenic patients was pursued in this group. The postoperative care was likewise identical. The preoperative preparation, however, was somewhat modified, as many of the patients were so severely agitated that it was necessary to administer sodium amytal, from 6 to 9 grains (0.3 to 0.5 Gm.), by mouth, sometimes augmented by the intramuscular injection of sodium amytal, prior to encephalography. By the preoperative use of sodium amytal the maniacal patients were readily managed even though not rendered somnolent.

Although many patients were recalcitrant, by virtue of the manic excitement, no mishap occurred during any of the encephalographic procedures. A number of the patients of this series had a complete remission after the encephalograms were taken, and made satisfactory adjustments.

With patience and perseverance it was possible to obtain the cerebrospinal fluid pressure when the manic patient was in repose. The depressed patient usually offered little difficulty in obtaining a pressure reading that was not influenced by straining or by some form of motor activity. The cerebrospinal fluid pressures were obtained in both the recumbent and the upright position and were determined in terms of millimeters of mercury. An effort was made to drain the cerebrospinal fluid system completely when possible. In only three cases was less than 100 cc. of cerebrospinal fluid removed; the largest quantity removed was 220 cc. In four cases there was failure in drainage of the ventricular system and replacement by air.

CEREBROSPINAL FLUID PRESSURES AND QUANTITY OF FLUID REMOVED

In the tabular summary it will be noted that the pressure while in a recumbent position in twenty-six instances, or 68 per cent, was 10 mm. of mercury or more. Normal cerebrospinal fluid pressure while in the recumbent position varies from 6 to 10 mm. of mercury, the latter being considered top normal. The highest pressure in the recumbent position was 20 mm. in one case of the series. In every case the pressure in the upright position was above 20 mm.; the normal pressure in the upright position ranges from 16 to 20 mm. In twenty-six cases the pressure in the upright position was 30 mm. or more, and in three cases the pressure reached 38 mm. These observations indicate an increased intracranial pressure in the majority of cases in the series. That some of the atrophic cortical changes are attributable to a chronic increased intracranial pressure must be borne in mind, although this factor is not the sole cause of cortical atrophy. This fact has been stressed by Winkelman and Fay and by Dixon and Ebaugh.

The cerebrospinal fluid system of the normal adult yields from 115 to 125 cc. of fluid when completely drained. One hundred and twenty-five cubic centimeters or more of cerebrospinal fluid was removed in twenty-six cases in this series. In eleven cases 150 cc. or more of cerebrospinal fluid was removed, and in one case, 220 cc. From these facts one may conclude, even without examining the encephalographic plates, that some degree of cortical atrophy or enlargement of the ventricular

system and cerebral cisterns existed in the majority of the patients examined. Atrophic changes may be present even in patients from whom less than the normal amount of fluid is obtainable on drainage, as we have previously illustrated.

The following tabulation is an analysis of the pressures and quantity of cerebrospinal fluid removed in the thirty-eight cases of the series.

I. Cerebrospinal fluid pressure in millimeters of mercury		
A. Recumbent position		
(1) Below 10		12
(2) 10 or above		26
B. Upright position		
(1) Below 20		0
(2) 20 or above		38
(3) 30 or above		26
(4) 38		3
II. Quantity of cerebrospinal fluid drained		
A. Less than 100 cc.		3
B. 125 cc. or more		26
C. 150 cc. or more		11
D. 200 cc. or more		3
E. 220 cc.		1

The encephalographic observations are as follows:

I. Ventricular system		
A. Lateral ventricles		
(1) Normal size		11
(2) Dilated		22
(*a*) Slightly	14	
(*b*) Moderately	6	
(*c*) Considerably	2	
(3) Asymmetrical		11
(*a*) Left greater than right	7	
(*b*) Right greater than left	4	
(4) Incompletely drained		2
(5) Failure to drain		3
B. Third ventricle		
(1) Normal size		18
(2) Dilated		15
(*a*) Slightly	11	
(*b*) Moderately	3	
(*c*) Considerably	1	
(3) Incompletely drained		1
(4) Failure to drain		4
C. Fourth ventricle		
(1) Normal size		18
(2) Dilated		14
(*a*) Slightly	9	
(*b*) Moderately	5	
(*c*) Considerably	0	
(3) Failure to drain		6

II. Cortical subarachnoid channels
- A. Normal 0
- B. Dilated 38
  - (1) Uniformly 6
  - (2) Irregularly 32
- C. Absence of air markings
  - (1) Diffuse (with occasional dilated channels)..... 6
  - (2) Irregular (patchy)..... 26
- D. Occipital lobe involved..... 7
- E. Insulae of Reil prominent..... 17
  - (1) Asymmetrical 5
- F. Sulcus cinguli prominent..... 10
- G. Sulcus callosi prominent..... 8

III. Cisterns
- A. Basal cisterns (cisternae chiasmatis, interpeduncularis, pontis and magna)
  - (1) Normal 22
  - (2) Enlarged 16
- B. Cisterna intercommunicans enlarged..... 3
- C. Cisterna venae magnae cerebri enlarged..... 6

IV. Cerebellar folia very prominent (atrophy)..... 3

V. Normal encephalogram..... 0

COMMENT

A review of the summary will show that the degree of pathologic change revealed by the encephalograms and the quantity of cerebrospinal fluid drained are not in proportion to the length of the history of manic-depressive psychosis or to the number of attacks. In fact, none of the factors enumerated seem to bear any relation to the encephalographic findings in what could be termed a definite ratio. Thus, in cases 43, 69, 75, 86, 97 and 104, in which the duration of the manic-depressive cycle had been, respectively, twenty, fifteen, twelve, eight and a half, seven and a half, sixteen and sixteen years, with more than one attack in each case, the amount of cerebrospinal fluid obtained varied from 100 to 145 cc. The encephalographic plates showed varying degrees of cortical atrophy and variations in the ventricular and cisternal patterns and arachnoidal adhesions. In cases 81, 100 and 103, in which the duration of the manic-depressive cycle had been, respectively, eight, eight and ten years, with more than one attack in cases 81 and 103, the quantity of cerebrospinal fluid removed varied from 150 to 210 cc.; in these cases there was considerable alteration in the cerebral architecture. The encephalographic findings in cases with a history of manic-depressive psychosis for over seven years show a wide variation.

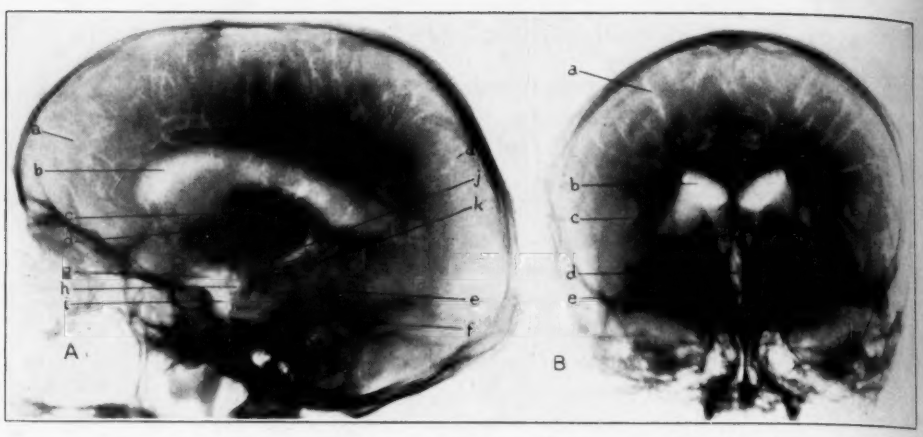

Fig. 1.—*A*, lateral encephalogram (by Dr. Matthew T. Moore, service of Dr. Temple Fay, Temple University Hospital) of a white girl, aged 18. This encephalogram presents an essentially normal appearance and may be used for comparison with the following series. At *a* the size and distribution of the normal subarachnoid channels are seen; *b* indicates the lateral ventricles; *c*, the foramen of Monro; *d*, the lateral projection of the third ventricle; *e*, the aqueduct of Sylvius; *f*, the fourth ventricle; *g*, the cisterna chiasmatis; *h*, the cisterna interpeduncularis; *i*, the cisterna pontis; *j*, the cisterna intercommunicans, connecting the cisterna interpeduncularis and the cisterna venae magnae cerebri; *k*, the cisterna venae magnae cerebri. The cortical air markings, extending from *a* to *a*, are not prominent beyond the parieto-occipital sulcus; they are of uniform caliber throughout. *B*, postero-anterior view of the same patient as in *A*. The ventricular shadows are normal in size and position, and the subarachnoid channels are normal in size and distribution: *a*, normal subarachnoid air markings; *b*, lateral ventricle; *c*, faintly discernible insula of Reil (normal); *d*, third ventricle; *e*, fourth ventricle.

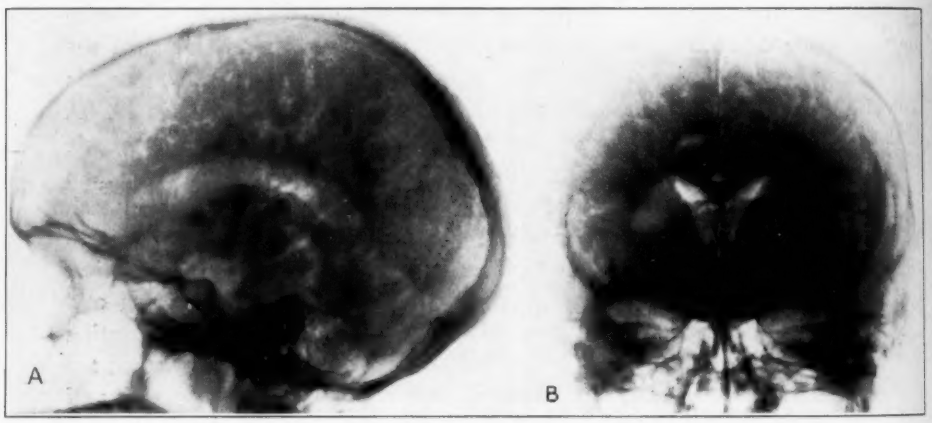

Fig. 2 (case A 1).—*A*, lateral view. The air markings are only slightly increased in size and are uniform. The ventricular system and basal cisterns are of normal size and contour. *B*, postero-anterior view. The cortical pathways appear to be only slightly increased in size; the sulcus callosi is prominent; the ventricles are normal in every respect.

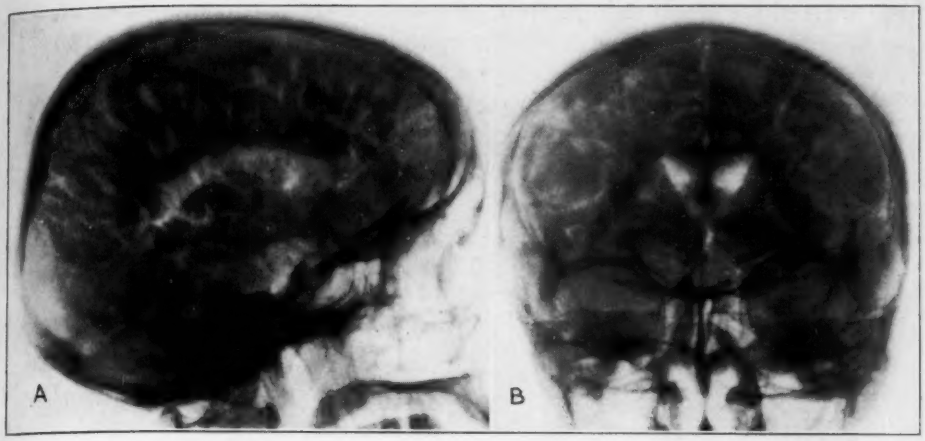

Fig. 3 (case 71).—*A*, lateral view. The cortical air markings are considerably enlarged, and involve the frontal, parietal and occipital lobes; in the central and postcentral areas near the vertex there is an absence of air markings. *B*, postero-anterior view. Considerable cortical atrophy is evidenced by the increased size of the air markings; the insulae of Reil are prominent.

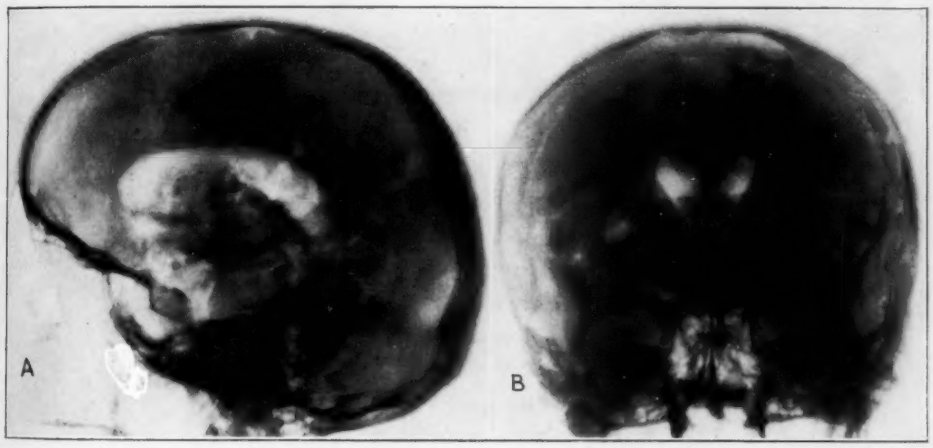

Fig. 4 (case 87).—*A*, lateral view. The cortex reveals an almost complete absence of air markings except for one or two enlarged channels in the post-parietal area; the ventricular system and basal cisterns are moderately enlarged. *B*, postero-anterior view. There is a complete absence of air markings over the cortex; the lateral ventricles are enlarged, with a slight degree of asymmetry; the insulae of Reil are prominent, the left more so than the right.

On the other hand, in some cases of comparatively short duration marked pathologic changes were seen in the encephalograms. Cases 22, 77 and 92, with manic-depressive episodes lasting fifteen months, two and a half and two and a half years, respectively, considerable changes were evident in the encephalograms, and there were drained in these cases 220, 215 and 190 cc. of cerebrospinal fluid, respectively.

The marked variability of the cerebral patterns is indicated in the accompanying illustrations. Figure 2 (case A 1) reveals the only encephalogram in the series that approximates the normal. The cortical sulci, however, are slightly larger than the size conceded to be normal by the Committee on the Standardization of Encephalography. The duration of the psychosis in this patient had been two years, with one

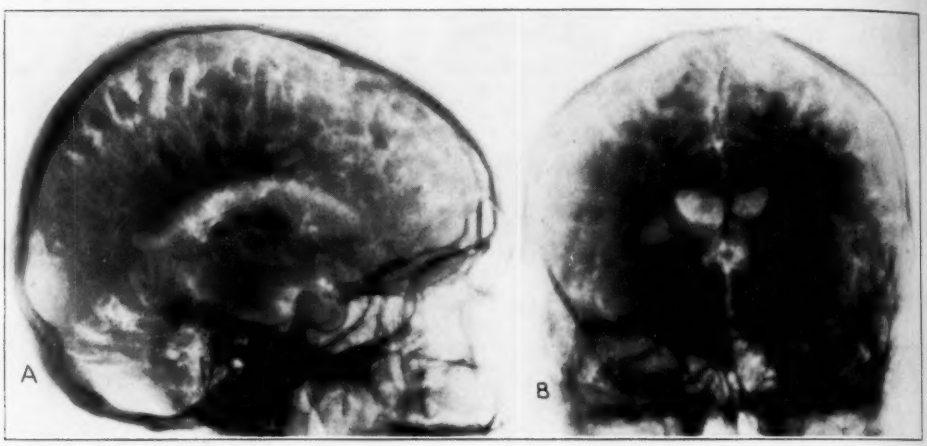

Fig. 5 (case 92).—*A*, lateral view. The markedly dilated air channels indicate fairly extensive cortical atrophy involving the frontal and parietal lobes; the lateral ventricles are slightly increased in size, and the cerebellar folia stand out prominently, indicating cerebellar atrophy. *B*, postero-anterior view. There is considerable cortical atrophy bilaterally; the sulcus cinguli and the insulae of Reil are prominent.

remission. It will be noted that, although only 120 cc. of cerebrospinal fluid was removed, the cerebrospinal fluid pressure was 14 mm. in the recumbent position and 32 mm. of mercury in the upright position.

Figure 3 (case 71) shows a more advanced degree of cortical atrophy than the preceding illustrations; the encephalograms are from a woman, aged 40, with a manic-depressive episode of one year's duration.

Figure 4 (case 87) presents a totally different picture from the foregoing views. There is an almost complete absence of air over the cortex, indicating the presence of an obstruction to the cortical pathways, in the

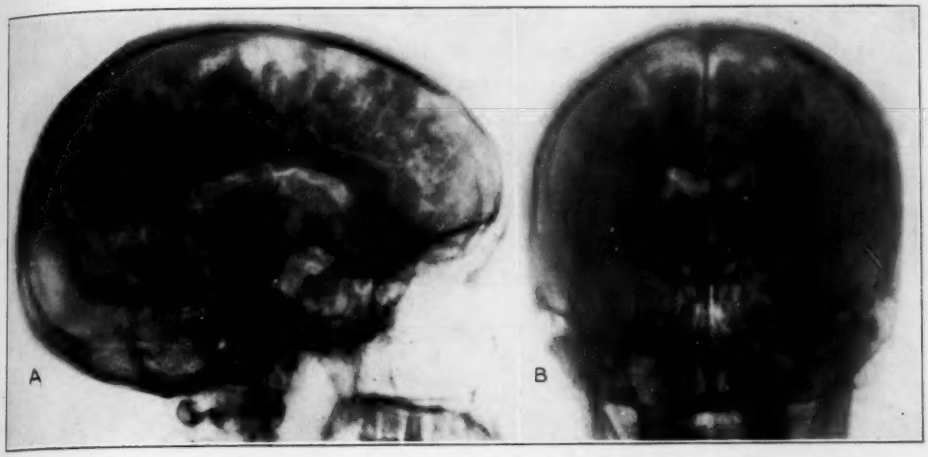

Fig. 6 (case 96).—*A*, lateral view. The patchy distribution of cortical atrophy is noticeable over the frontal and parietal lobes, with large laked areas over the vertex in the region of the precentral and central areas. Some areas are devoid of air markings; the lateral ventricles and basal cisterns are slightly increased in size. *B*, postero-anterior view. The air markings over the vertex are enlarged, and the interhemispheric air is increased.

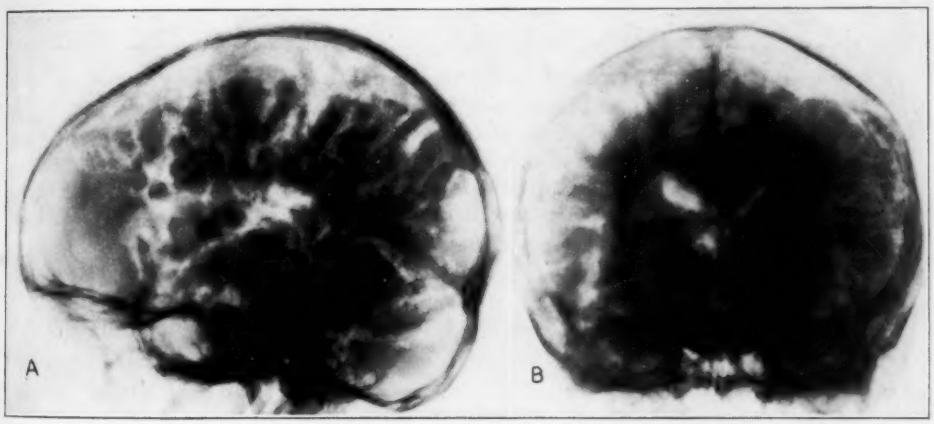

Fig. 7 (case 100).—*A*, lateral view. There are extensive areas of atrophy involving the frontal, parietal and occipital lobes; the cerebellum shows atrophic changes. *B*, postero-anterior view. There is extensive atrophy involving the lateral aspects, and in this view involvement of the temporal lobe can readily be seen; the insulae of Reil are prominent, particularly the left; there is an extradural collection of air over the right vertex which has caused a depression of the right lateral ventricle, and the cisterna venae magnae cerebri is enlarged.

form of (1) arachnoidal adhesions, (2) a change in the consistency of the cerebrospinal fluid or (3) temporary edema resulting from alterations in the vasculature incident to changes in intracranial pressure induced by encephalography, producing an obstruction to the egress of fluid and the ingress of air over the cortex. Cortical atrophy probably existed in this case, for the few air markings shown are definitely enlarged.

Figures 5 (case 92) and 7 (case 100) show how extensive the cortical changes may become; one case was only of two and a half years' duration, the other of eight years' duration.

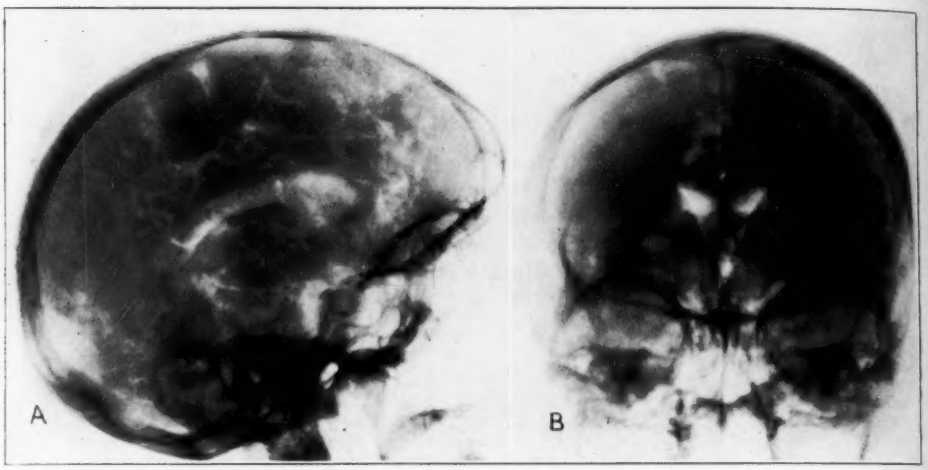

Fig. 8 (case 102).—*A*, lateral view. There are scattered, dilated air markings over the frontal, parietal and preoccipital lobes, with areas devoid of air markings in the frontal and parietal lobes; the lateral and third ventricles are of about normal size, with the fourth ventricle slightly increased in size. *B*, the air markings present are irregularly distributed and slightly dilated; there is for the greater part an absence of markings; the lateral ventricles are normal and symmetrical; the insulae of Reil are visualized on each side; the sulcus cinguli can be readily distinguished.

In figures 6 (case 96) and 8 (case 102) are illustrated the combined picture of areas depicting cortical atrophy and areas devoid of air markings, indicating the pathologic changes described for case 87.

The encephalograms in all thirty-eight cases reveal changes comparable with those shown in the representative illustrations. It would be foolhardy to attempt to formulate or propose broad generalizations on the basis of this group. However, it is apparent from the encephalograms that the cerebral architecture in every case is in some way abnormal, and it is fair, therefore, to assume that some organic change exists.

CONCLUSIONS

1. The cerebrospinal fluid pressures, in terms of millimeters of mercury, have in the majority of cases been top normal or higher, indicating the presence of the factor of chronic increased intracranial pressure.

2. The quantity of cerebrospinal fluid removed in the majority of cases has indicated varying degrees of cortical atrophy and enlargement of the ventricular system and cisterns.

3. No definite cerebral pattern is obtained in a sufficient number of cases to be characteristic.

4. The encephalographic pathologic condition is manifested in the following ways: (1) cortical atrophy of varying intensity; (2) enlargement of the ventricular system; (3) asymmetry of the lateral ventricles; (4) absence of cortical air markings; (5) enlargement of the cisterns; (6) island of Reil atrophy; (7) enlargement of the sulcus callosi and sulcus cinguli; (8) increased interhemispheric air, and (9) cerebellar atrophy.

5. None of the encephalographic films showed a normal cerebral pattern.

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SCLEROTIC ATROPHY OF THE CEREBELLUM

REPORT OF TWO CASES

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Unlike the rest of the brain or the spinal cord, the cerebellum may exhibit a condition rather common in this organ and collectively classified as atrophy. Cerebellar atrophies are for the most part secondary to some inflammatory, degenerative or vascular disease process, in contrast to agenesis, malformations, maldevelopments or aplasia, in which the atrophy is primary. Of the numerous classifications of cerebellar atrophies, that proposed by Marie, Foix and Alajouanine [1] seems to me the most rational. These authors recognize three large groups: (1) congenital atrophies, which occur mainly in idiots and usually affect the lateral lobes of the cerebellum; (2) familial atrophies, represented by the cerebellar heredo-ataxia of Marie, and (3) a large group of acquired cerebellar atrophies, with which are included the olivopontocerebellar type of Dejerine and Thomas, the atrophy of the dentate system of Ramsay Hunt, and a type variously described and termed by them late cerebellar atrophy, predominatingly of the cortex. According to this classification, the cerebellar atrophies occurring in the late infantile type of amaurotic family idiocy or in Niemann-Pick's disease should be referred to group 2, while the cerebellar atrophies occasionally observed in juvenile dementia paralytica or other inflammatory and degenerative states should not be labeled as typical. In the aforementioned conditions, the atrophy does not dominate the pathologic picture, which, in dementia paralytica, for instance, is overshadowed by marked changes elsewhere in the central nervous system. The term cerebellar atrophy should be used only for conditions in which it dominates the pathologic picture, provided the cerebellum is well developed before atrophy sets in. Regardless of the type and the etiology, the characteristic feature of cerebellar atrophy is degeneration of the cerebellum associated, in the advanced, old cases, with the formation of

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1. Marie, P.; Foix, C., and Alajouanine, T.: De l'atrophie cérébelleuse tardive à prédominance corticale (atrophie parenchymateuse primitive des lamelles du cervelet; atrophie paléocérébelleuse primitive), Rev. neurol. **38**:849 and 1082 (July) 1922.

patches of sclerosis. For this reason, the term cerebellar sclerosis has been much in favor, especially in the older literature. The various acquired forms of this morbid condition differ from one another in the extent of the degeneration of the cerebellar tissues and the presence or absence of involvement of adjacent or remote structures. For instance, in the olivopontocerebellar form of Dejerine and Thomas or the olivorubrocerebellar type of Lejonne and Lhermitte there is, as the names imply, involvement not only of the cerebellum but also of the pons, olivary bodies and red nuclei, while in the form termed by Marie, Foix and Alajouanine the late cerebellar type, changes are present only in certain parts of the cerebellum; in the lobus quadrilateralis and the lobus semilunaris of the upper surface and in some parts of the superior vermis. This type has also been described as lamellar atrophy (André-Thomas [2]), primary parenchymatous cerebellar atrophy with cortical localization (Rossi,[3] Archambault [4] and Parker and Kernohan [5]), cerebellar astasia-abasia (Lhermitte [6]), unilateral atrophy of the cerebellum (Lannois and Paviot [7]), sclerosis of the cerebellum and many other conditions less well known.

In some instances neither the upper nor the inferior vermis is involved, and the changes are confined to the upper or anterior surface of the lateral lobes of the cerebellum (neocerebellum). Such cases, two of which are the subject of this paper, are comparatively rare and present interesting pathologic features.

REPORT OF CASES

CASE 1.—*History and Course.*—A white woman, aged 27, whose personal and family history is irrelevant, was admitted to the John B. Murphy Hospital on Oct. 28, 1932, because of general nervousness, asthenia, sore throat and swelling of the neck and cheek. She had been in good health until four years prior to her entrance into the hospital, when she became irritable and restless. A diagnosis of hyperthyroidism was made, and though an operation had been performed four years previously, the condition grew worse. In July, the patient had had several

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attacks of sore throat, which were accompanied by severe pain in the ear and swelling and stiffness first of one and later of the other side of the neck, for which she sought admission to the hospital.

Examination.—The patient was well nourished, but anemic; the musculature was flabby; the parotid and lymph glands of the posterior cervical region were swollen, and a large linear scar was present on one side of the neck (which side is not recorded). There were no anomalies of gait or speech, and the mental condition was normal. A slight exophthalmos was noticeable, but the ocular nerves as well as other cranial nerves exhibited no signs of paralysis. The pupils reacted well to light and in accommodation, and the reflexes as well as the visceral organs were entirely normal. The temperature was 101.2 F.

Laboratory Examinations.—The blood contained: hemoglobin, 50 per cent; red cells, 2,760,000, and white cells, 90,500, of which 13 per cent were polymorphonuclears, 8 per cent lymphocytes, 3 per cent large mononuclears, 4 per cent eosinophilic myelocytes, 70 per cent neutrophilic myelocytes and 2 per cent basophilic myelocytes. On November 18, there were: 31 per cent hemoglobin; 2,680,000 red cells, and 56,000 white cells, of which 60 per cent were neutrophilic myelocytes. Examination of the urine revealed: albumin, 2+; many squamous epithelial cells mixed with white and red cells, and numerous coarse granular casts. Smears from the mouth revealed fusiform bacilli and gram-positive cocci, and cultures exhibited pneumococci and streptococci.

Comment.—The foregoing data show that the patient suffered from a severe, toxic-infectious state, which was probably due to leukemia and indirectly affected the nervous system, causing irritability and restlessness. There was nothing in the history that was even suggestive of an organic lesion of the peripheral or central nervous system, including the cerebellum.

Necropsy.—Necropsy was performed by Dr. Nowakowsky, who summed up the gross pathologic findings as: leukemic infiltrations of the liver and kidneys; adenopathy of the neck and retroperitoneal lymph nodes; glomerulonephritis; brown atrophy of the heart; acute swelling of the spleen; edema of the brain, which weighed 1,200 Gm., the dura of which was tense and the opening of which caused a large amount of fluid to escape; multiple subcutaneous and submucous hemorrhages, and decubitus.

There was marked atrophy of the right lobe of the cerebellum (fig. 1), which was hard to the touch and in which the areas in the transverse section along the large horizontal fissure appeared pale and shrunken. It measured 2.5 by 1.5 cm., while the left measured 4.5 by 3.5 cm. The atrophied, pale, shrunken area included the entire superior semilunar lobule (fig. 2 *A*) and a small portion of the quadrilateral lobule. The lamellae of the affected part of the cerebellum, even with the pia not detached were sharply defined even macroscopically, as if divided from one another by widened sulci. The upper and lower worms were of normal color; their white and gray matter were sharply delimited and of normal consistency and volume.

The left cerebellar lobe, as well as the cerebral hemispheres with their ventricles, basilar nerves and blood vessels, exhibited no changes.

Microscopic Observations.—Sections stained with the Weigert-Pal method demonstrated well the condition of the affected parts (fig. 3). Only a very small portion at *A* was normal, and the rest of the lamellae, gray as well as white substance, were entirely colorless. The nucleus dentatus, its fleece, the semicircular fibers, the spinocerebellar tract (corpus restiforme) and the fibers emanating from

the dentate nucleus (brachia conjunctiva) were not involved. The individual leaflets were greatly reduced in size and shrunken. The majority hardly resembled histologically those of a normal cerebellum. The molecular layer, the Purkinje cells and the granular layer were for the most part replaced by

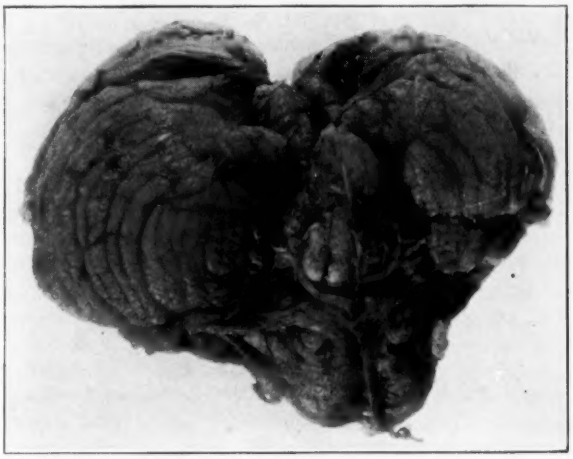

Fig. 1.—The inferior surface of the cerebellum. The right lobe is smaller than the left.

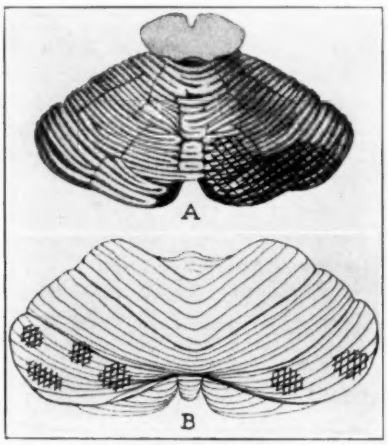

Fig. 2.—*A* (case 1), the shaded area indicates the affected semilunar lobule and a part of the quadrilateral lobule which are stained and pictured in figure 3. *B* (case 2), the patches are shown as shaded areas over the superior surfaces of the semilunar lobes.

neuroglial tissue and were reduced in size. In short, there was what conveniently may be called a global atrophy of parts of the cerebellum, for the white substance of some lamellae, bordered by the degenerated granular layer, was also atrophied and transformed into a glial tissue scar (fig. 4 *A*). The normal constituents of the

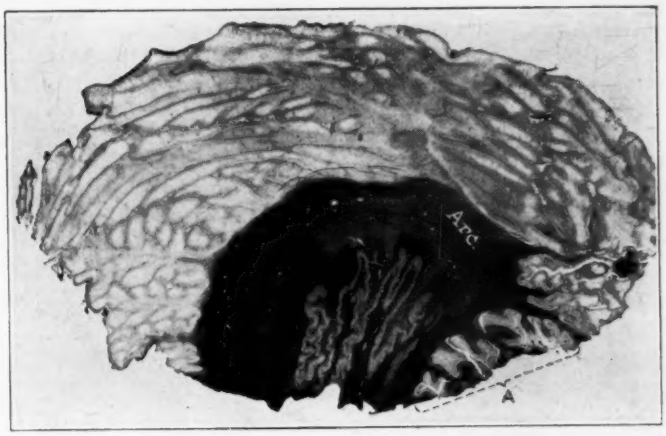

Fig. 3.—Degenerated parts of the cerebellum indicated by a shaded area in figure 2 *A*; *A*, preserved or normal portion, and *Arc*, semicircular fibers. Pal-Kultschitzky stain.

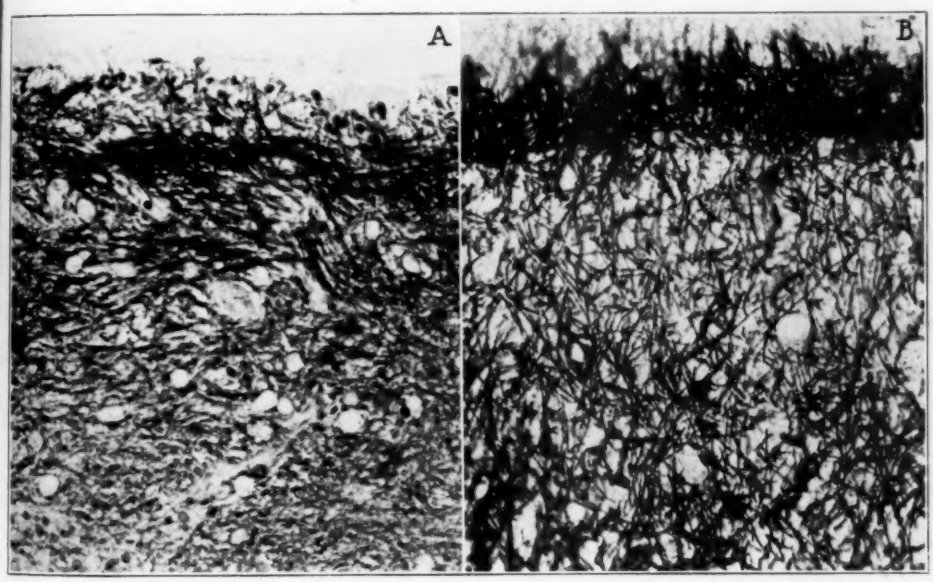

Fig. 4.—*A*, the degenerated parts of the cerebellum are transformed into a glial tissue scar. The upper, transverse, dark-stained fibers are tangential fibers traversed in places by radial fibers, forming a whorl of glia fibers. Holzer stain; *B*, brain of a patient with Pick's disease (Braunmühl). Both pictures should be compared with figure 8 *B*, showing a normal cerebellum.

molecular layer—the superficial stellate and the basket (deep stellate) ganglion cells with their axons and dendrons, the ramifications of the cells of the granular layer with their parallel fibers and the dendrons of the Purkinje cells and climbing fibers—were absent. They, as well as the white substance, were replaced by a thick feltwork of glial tissue in which glia nuclei were scattered and mixed with numerous blood vessels (fig. 5). The glia fibers were delicate and unusually thin; occasionally they exhibited a cytoplasmic astrocyte. They were mostly interwoven, but some formed thick tangential bands that ran parallel to the surface of the cerebellar cortex, as if marking the course of the tangential nerve fibers which they replaced. This was especially well seen in the upper marginal or subpial layer of the cerebellum (fig. 4*A*). Other glia fibers had a radial course; that is, they extended from the layer of the Purkinje cells across the molecular layer.

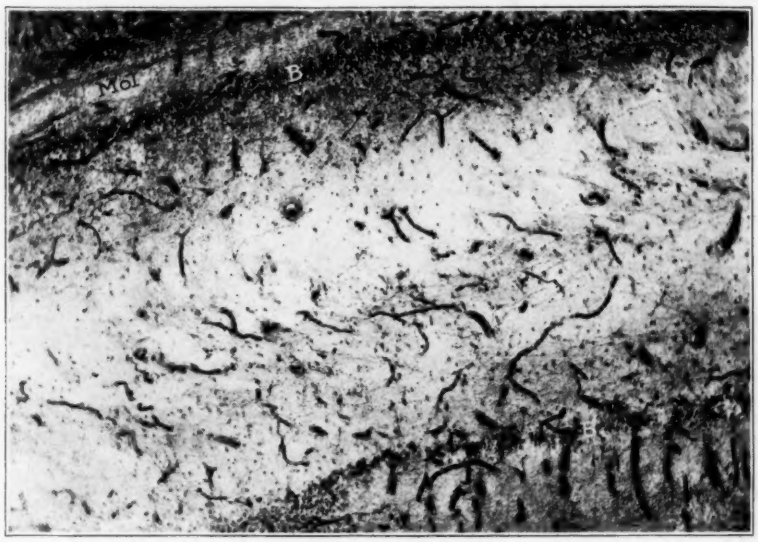

Fig. 5.—An atrophied leaflet. *Mol* indicates the molecular layer, reduced in size and consisting of glia fibers; *B*, Bergmann's glia cells, with a complete absence of Purkinje cells; the layer below the upper *B* is the granular layer devoid of ganglion cells, but rich in blood vessels, which are also numerous in the white medullary substance occupying the entire center of the picture. Cajal's corrosive gold sublimate stain.

These fibers, known as Bergmann's glia fibers, originate from the glia cells of the Purkinje cell layer, commonly described as Bergmann's cells or the epithelial cells of Golgi. The density of the glial network was so great that it was not possible to demonstrate the generally accepted relationship between the glia fibers and the Bergmann glia cells. The bands or bundles of glia fibers faithfully reproduced the course and arrangement of the destroyed nerve fibers and of the ramified dendrons of the Purkinje cells, giving the picture of so-called isomorphous gliosis. However, the main mass of the glial tissue of the molecular layer also exhibited whorls of glia fibers, an irregular dense network (anisomorphous gliosis) which was

traversed by radial bundles (fig. 4 *A*) and, as mentioned, exhibited a scarcity of glia nuclei and numerous blood vessels. In short, the entire molecular layer was transformed into a solid glial tissue scar.

The same was true of the other constituents of the cortical layers of the cerebellum—the Purkinje and the granular cell layers. The Purkinje cells were absent in the affected leaflets (fig. 6), and when present were often dislocated or displaced into the molecular layer (fig. 7 *P*), as has again been emphasized of late by Huber [8] and Kirschbaum and Eichholz.[9]

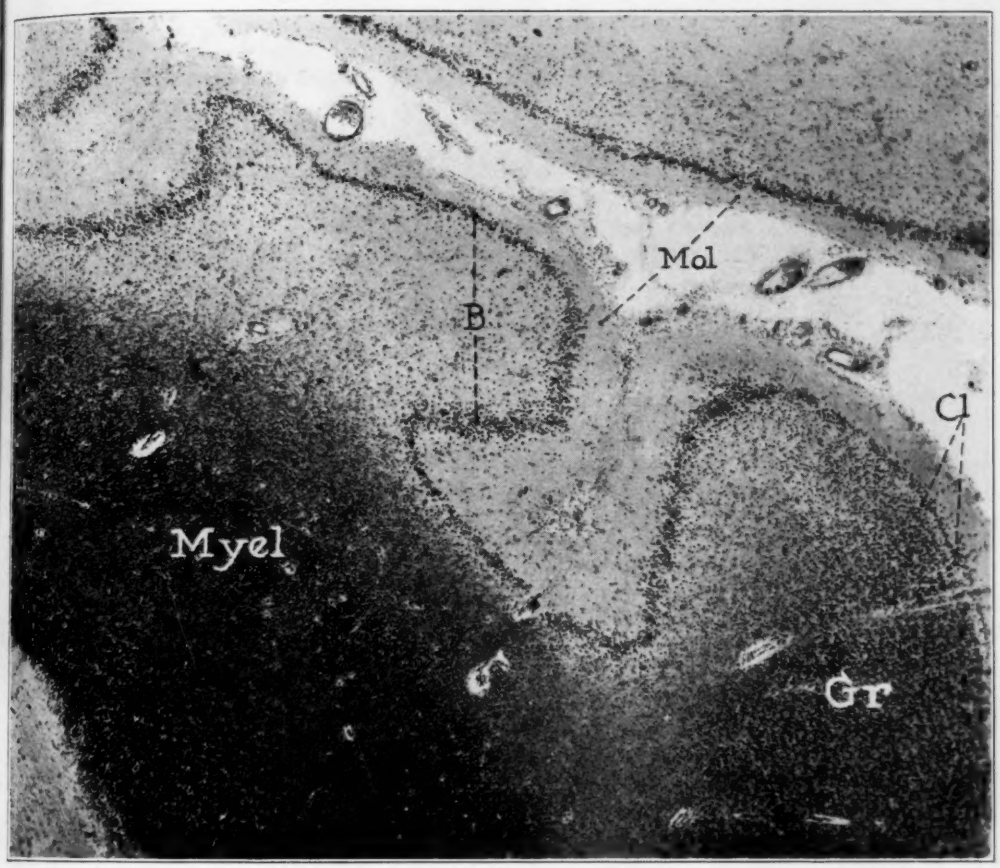

Fig. 6.—An atrophied leaflet of the cerebellum. *Mol* indicates the molecular layer; *B*, Bergmann's glia cells; *Cl*, "cleavage," a colorless area between the Bergmann glia cells and the granular layer (*Gr*) below; *Myel*, the medullary white fibers of the leaflet; the granular layer containing the letter *B* is entirely devoid of granular ganglion cells, which are abundant in the area marked *Gr*. Pal-Kultschitzky stain counterstained with van Gieson's stain.

8. Huber, W.: Partielle und generalisierte Kleinhirnsklerosen, Jahrb. f. Psychiat. u. Neurol. **37**:625, 1929.

9. Kirschbaum, M., and Eichholz, A.: Ueber primäre Kleinhirnrindenatrophie, Deutsche Ztschr. f. Nervenh. **125**:21, 1932.

An additional phenomenon deserves attention. The displaced cell bodies, which were broken up into small fragments and granules, exhibited a great affinity for hematoxylin, especially when they were stained with the myelin sheath staining method of Weigert and Pal or its modifications. When thus stained, the Purkinje cells became unusually promiscuous, and not only the cell bodies and dendrons but also the axons became densely impregnated with the stain. The Purkinje cells appeared dark and granular (fig. 8 *A*) and overshadowed all other structures in the visual field. This was especially striking when these densely impregnated cell bodies were contrasted with those of normal lamellae. As figure 8 *B* shows, normal lamellae exhibit rather pale bodies possessing a visible nucleus and hardly any processes, while the pathologic cells, including their processes, are uniformly dark. No nucleus can be discerned in them; the processes are thick, granular

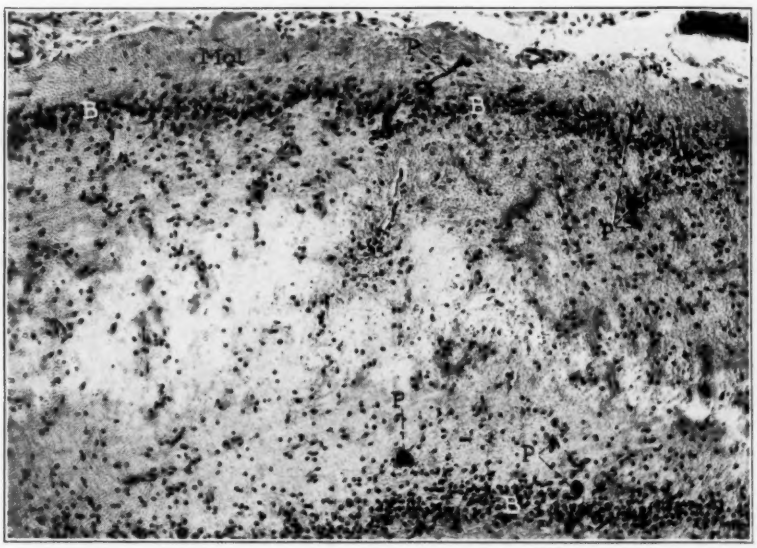

Fig. 7.—Displaced calcified Purkinje cells (*P*), which are dark and homogeneous. *Mol* signifies molecular, and *B*, Bergmann's glia cells; normal Purkinje cells are absent, and rarefaction of the white medullary fibers of the leaflet (in the center of the picture) is marked. Pal-Kultschitzky stain.

and broken up. Since the granules and the homogeneous dark cell bodies could be dissolved in solutions of hydrochloric acid, the changes are to be considered those of calcification.

In specimens in which the Purkinje cells are absent, there is present only a thin band of nuclei (fig. 6), which at first glance impresses one as a granular layer reduced in size. One can discern in it a colorless band (fig. 6 *Cl*) situated between the Bergmann glia cells and the granular cell layer below. This band has been described by Archambault [4] as cleavage, by Schroeder and Kirschbaum [10] as

10. Schroeder, A. H., and Kirschbaum, W.: Ueber eigenartige degenerative Erkrankungen des Zentralnervensystems mit vorwiegender Beteiligung des olivocerebellaren Systems und Grosshirnrindenveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:681, 1928.

artificial *Lücke* (defects) and by others as an artefact. It must be stated that it is not specific for the atrophies or any other pathologic conditions of the cerebellum. It may be present even in normal cerebellums, when it is probably produced by the action of the fixation fluids or is due to abnormal contractions of the glial tissue of the molecular layer. In an atrophied cerebellum in which the Purkinje cells have disappeared, it is natural to expect the space occupied by them to appear larger and for this reason pathologic. Equally misunderstood were the previously described Bergmann glia cells which, as explained, separate the granular layer from the molecular layer. Vogt and Astwazaturow [11] considered them embryonic ganglion cells; Lannois and Paviot,[7] who also classified them as ganglion cells (embryonic), termed them innominate elements, while Cajal [12] classified them as epithelial cells of Golgi, and Bériel [13] as glia cells. Like the

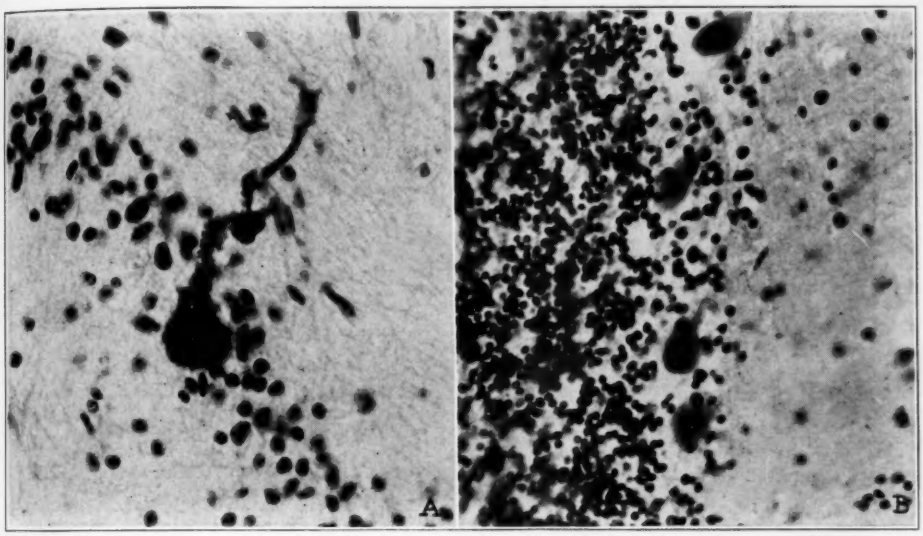

Fig. 8.—*A*, a calcified Purkinje cell in atrophic sclerosis of the cerebellum. The hematoxylinophilic granules are well seen, especially in the processes. The row of nuclei are Bergmann's glia cells. Pal-Kultschitzky stain; × 500. *B*, normal Purkinje cells of a preserved leaflet surrounded by Bergmann's glia cells and situated above the granular layer. Pal-Kultschitzky stain; reduced from a magnification of × 400. *B* should be compared with figure 4.

cleavage, they become especially promiscuous when the subjacent granular layer becomes atrophied. Then, as figure 6 shows, they are the only cell remnants in the cerebellar cortex. The few rows formed by them, which, as explained, impress

11. Vogt, H., and Astwazaturow, M.: Ueber angeborene Kleinhirnerkrankungen mit Beiträgen zur Entwickelungsgeschichte des Kleinhirns, Arch. f. Psychiat. **49**:75, 1912.

12. Ramon y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, translated by Azoulay, Paris, A. Maloine, 1911, vol. 2, p. 68.

13. Bérial, L.: Die sogenannte "äussere Körnerschicht" (Vogt und Astwazaturow) in akquirierten Kleinhirnerkrankungen, Arch. f. Psychiat. **51**:1080, 1913.

one at first as a granular layer reduced in size, are glia cells, for it is possible to demonstrate glia fibers emanating from them and traversing the molecular layer in a radial manner. In a normal granular layer these glia cells are also present, but they are overshadowed by the granular cell nuclei, and are intermingled with ganglion cells of the Golgi II type and numerous nerve fibers (mossy fibers) winding among dense rows of cells. No mossy fibers, Golgi cells or other ganglion cells were present in case 1, all having been replaced by a glial tissue scar.

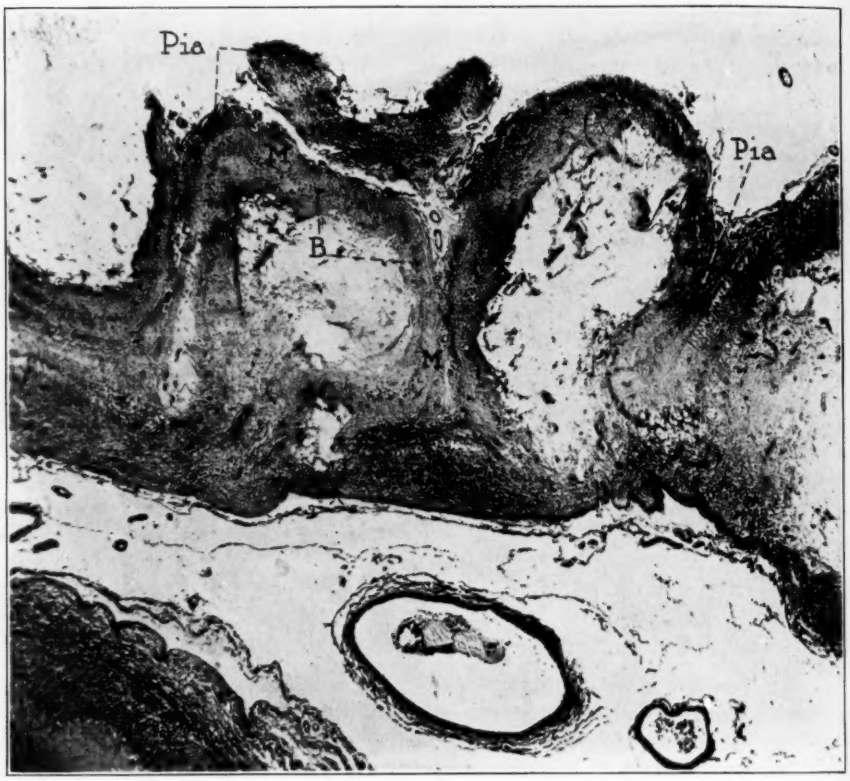

Fig. 9.—Advanced changes in the medullary white substance of degenerated cerebellar folia. *M* signifies the molecular layer; *B*, Bergmann's glia cells. The adhesions between the adjacent leaflets, with obliteration of the subarachnoid space, is well seen to the right and marked *Pia*. The glial tissue in the center of the leaflets appears torn. Bielschowsky stain.

Figure 7 shows an advanced degeneration of the white substance of the atrophied cerebellar leaflets. There were hardly any preserved nerve fibers; they had been replaced by a loose meshwork of glia fibers. As they did not take the myelin sheath stain they appeared colorless or, as they are customarily described, demyelinated. In some leaflets the glial meshwork was in the form of large cavities (fig. 9), as if it had been torn apart; the cavities often contained enormous quantities of blood vessels (fig. 5).

The blood vessels were always patent; their walls were thickened because of hyperplasia of the adventitial tunic. The collapsed adventitial spaces contained no lipoids; lipoids were absent also in the glial tissue, where, however, other catabolic products in the form of large accumulations of amyloid bodies were abundant. Amyloid bodies were also abundant in the sclerosed areas of the degenerated leaflets.

In some lamellae only a part of a leaflet was involved; in others the normal structure was preserved. In no instance was it possible to demonstrate transitional phenomena of nerve or cell degeneration, such as fragmentation of nerve fibers, neuronophagic phenomena or vacuolation or sclerosis of the ganglion cells. The changes were exclusively those seen in the last stages of nerve degeneration.

The pia-arachnoid over the sclerosed laminae of the cerebellum was hyperplastic and it obliterated the subarachnoid space (fig. 9). In some areas it appeared as a dense feltwork of connective tissue and was blended with the subjacent hyperplastic subpial glial layer and the sclerosed molecular zone of the cerebellum. The hyperplastic pia situated between adjacent leaflets also obliterated their interspaces and caused them to fuse (fig. 9). Only with the staining method of van Gieson was it possible in some instances to differentiate the feltwork of the hyperplastic pia from that of the glia of the cerebellum. Both the pia and the subjacent cerebellum appeared as one solid scar when stained with the method of Holzer or Bielschowsky, though the pia exhibited a much denser and more powerful network of fibers than the glia. Nowhere, however, was there in evidence an invasion of the cerebellum by the hyperplastic pia or vice versa; nor were there signs of inflammation, such as lymphocytes, plasma cells or vascular changes.

Microscopic studies of the cerebrum revealed scattered microscopic foci of softening and an occasional rarefaction—changes which had no relationship to those of the cerebellum, but which were most likely the result of the patient's severe toxic state.

The subarachnoid space of the brain was distended and contained numerous fibroblasts, polyblasts and histiocytes, many of which harbored granules of pigment. A similar condition was in evidence over the nonaffected portions of the cerebellum, and thus the subarachnoid strikingly differed from the cerebellar pia-arachnoid of the areas affected as previously described.

Changes occasionally found in the dentate nucleus (Spiller,[14] Kirschbaum and Eichholz) and in the afferent cerebellar systems were not present in this case.

In the second case the histologic changes were similar to those outlined in case 1; they were also present on the upper surface of the cerebellum, but bilaterally (fig. 1 *B*).

Case 2.—A white woman, aged 32, was admitted to the Kankakee State Hospital because of a disturbed mental condition, which was diagnosed as the hebephrenic type of dementia praecox. She had been married twice. She said that she had not had an infectious disease, but there was a somewhat doubtful history of alcoholism and of a gynecologic operation at the age of 25. She was irritable and quarrelsome, especially during the menstrual periods, when she was hypersexual. Once she had a severe epileptiform seizure, which was followed by violence and destructive tendencies.

At the age of 32 the patient was committed to the Kankakee State Hospital. Aside from indefinite hallucinations of reference and delusions of persecution, no

14. Spiller, W. G.: Four Cases of Cerebellar Disease (One Autopsy) with Reference to Cerebellar Hereditary Ataxia, Brain **19**:588, 1896.

anomalies were detected in the patient's physical and mental condition. As in the previous case, nothing indicated an involvement of the cerebellum or of other parts of the central nervous system. After an illness lasting six years, the patient died at the age of 36.

Necropsy.—This was performed by Dr. Gier and revealed bronchopneumonia, myocarditis, nephritis and a fatty liver. No macroscopic or striking microscopic changes were present in the cerebrum, but they were abundant in the cerebellum. The hemispheres, especially the right, were diminished in size and hard to the touch. In a horizontal section of the cerebellum along the sulcus transversus a number of circumscribed, uniformly pale foci of various sizes and shapes were present over the superior semilunar lobe and part of the quadrilateral lobes of the hemispheres. As in case 1, the flocculus, tonsils and entire inferior surface of the cerebellar hemispheres were not involved, nor did the superior or inferior vermis exhibit anomalies. The condition of the cerebellum was almost a duplicate of that described by Sommer in 1884.[15]

Microscopic Observations.—These were identical with those described in case 1. There were: complete degeneration of the ganglion cells and nerve fibers of a few cerebellar folia, including the white substance; a marked hematoxylinophilic state of the ganglion cells; extensive proliferation of the glia, with the formation of scar tissue and numerous corpora amylacea; absence of inflammatory phenomena; hyperplasia of the pia-arachnoid, which almost fused with the underlying hyperplastic layer of the cerebellum; preservation of the dentate nucleus, various peduncles of the cerebellum, the nucleus ruber, the olivary bodies and the Bergmann cells. It should again be emphasized that though the changes were marked and even more widespread than in case 1, no clinical symptoms of a cerebellar lesion were present.

COMMENT

In the two cases described the pathologic process was local; that is, it was limited to a few lamellae of the cerebellum. It was of the nature of a complete degeneration of all of the nerve elements of the affected portions, which were replaced by glial tissue. The morbid process was confined to a few scattered islands, and there were no histologic signs of a recent progressive invasion of new territories of the cerebellum. The pathologic process evidently came to a standstill; it became extinct. Its outstanding character was an exclusive involvement of the ganglion cells of a few lamellae of the cerebellum—the Purkinje cells, the granular layer cells, the stellate cells of the molecular layer, the Golgi cells and all their dendrites and axons. As cases have been described (Rossi,[3] Jelgersma[16] and Parker and Kernohan[5]) in which only the Purkinje cells were degenerated, one must consider them the most vulnerable elements, for they are affected early and constantly. Their destruction, especially when it involves also the other ganglion cells which with their processes constitute the bulk of the cerebellar cortex,

15. Sommer, W.: Zur Casuistik der Kleinhirnsklerose, Arch. f. Psychiat. **15**:252, 1884.

16. Jelgersma, G.: Eine Systemerkrankung im Kleinhirn, Jahrb. f. Psychiat. u. Neurol. **25**:42, 1920.

explains well the transformation of the latter into a glial tissue scar. The same is true of the white substance of the cerebellar leaflets. It is made up of the axons of the Purkinje cells, and their destruction is the cause of the degeneration of the white or medullary substance. As hinted by Marie, Foix and Alajouanine, the morbid process in the condition under discussion is not unlike that observed in amyotrophic lateral sclerosis. In both atrophy of the cerebellum and amyotrophic lateral sclerosis the pathologic process is nuclear. In amyotrophic lateral sclerosis the system of ganglion cells of the nuclei of the motor cranial and spinal nerves is involved, while in this form of cerebellar atrophy the degeneration involves the system of Purkinje and other ganglion cells which make up the strata of this organ. In both morbid conditions the efferent nerve fibers are involved, but only secondarily as the result of a degeneration of the primary ganglion cells. In amyotrophic lateral sclerosis the efferent fibers are the pyramidal and the motor peripheral (cranial and spinal) nerves; in this form of cerebellar atrophy they are the tangential, parallel and white fibers proper of the lamellae. As the mossy fibers and the climbing nerve fibers were, in my cases, also completely degenerated, these fibers are probably also efferent and not afferent, as has been considered by the majority of investigators (Brouwer,[17] Jelgersma [18] and others). As in amyotrophic lateral sclerosis, degeneration of the gray substance in this form of cerebellar atrophy is primary and independent of vascular, meningeal or inflammatory factors. Nor are the changes to be considered as of the nature of agenesis or aplasia of the cerebellum, as in these conditions parts of the organ either are not fully developed or are maldeveloped, but the histologic structure is preserved. The changes also differ from those seen in cerebellar atrophies occurring in some forms of amaurotic family idiocy, Niemann-Pick's disease and Marie's hereditary cerebellar ataxia. In these, other changes are present which are so typical that a differential diagnosis is not difficult. On the other hand, they are entirely similar to the changes described in the olivopontocerebellar and olivorubrocerebellar atrophies from which, as has been pointed out, they differ only quantitatively. As the changes in the latter two conditions are also those of sclerosis, the name cerebellar sclerosis used so much in the older literature and, more recently, by Obersteiner and his school would be less proper than the name late cerebellar atrophy, which was proposed by Marie, Foix and Alajouanine, especially if one considers that the morbid process may not show as sclerosis at all but merely as atrophy of the Purkinje cell layer.

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17. Brouwer, B.: Ueber Hemiatrophia neocerebellaris, Arch. f. Psychiat. **51:** 539, 1913.

18. Jelgersma, G.: Das Kleinhirn in anatomischer, physiologischer und pathologischer Hinsicht, Jahrb. f. Psychiat. u. Neurol. **44:**33, 1932.

The islands of sclerosis unquestionably much resemble those of multiple sclerosis. The question arises whether it is permissible to classify cerebellar cortical atrophy as multiple sclerosis. In the latter condition the changes are primarily and exclusively in the white matter; in cerebellar atrophy they are, in contrast, in the gray matter and involve the white matter secondarily. Though the ultimate patches of multiple sclerosis may be entirely similar to those of cerebellar cortical atrophy, they usually contain normal axons and, as a rule, exhibit evidences of recent nerve degeneration. These phenomena are foreign to cerebellar cortical atrophy, in which the degenerative process, as has been pointed out, is extinct and does not progress until death as is the case in multiple sclerosis. The only morbid condition of the central nervous system which is fully analogous to cerebellar cortical atrophy macroscopically and microscopically is Pick's disease (fig. 4 *B*). In Pick's disease the lesion is in the cerebrum; it is also circumscribed and confined to one or more lobes, or to a portion of a lobe in which the ganglion cells and nerve fibers are degenerated and the glia is proliferated, causing shrinkage of the cortex; there is also excessive vascularization, sclerosis causing hardness of the tissues and absence of inflammatory phenomena. In both cerebellar atrophy and cerebral atrophy or Pick's disease the nerve changes are degenerative and are either of indefinite etiology or partial manifestations of such chronic conditions as arteriosclerosis or other degenerative vascular diseases. However, neither Pick's disease nor cerebellar cortical atrophy is directly due to such vascular disturbances as arterial thrombosis (Taft and Morse [19]), an inflammatory vascular process (Pollak [20]), atresia of the blood vessels (Archambault [4]) or nutritional disturbances (Huber [8]), for on the basis of such vascular factors it would not be possible to explain the exclusive and irregular or scattered involvement of the ganglion cells, aside from the fact that the blood vessels in the conditions under discussion are practically normal. For like reasons chronic meningitis (Baird [21]) cannot be considered the cause of the cell degeneration, while the theory of agenesis advocated by Lannois and Paviot [7] is not applicable, for cerebellar atrophy occurs in brains that are fully developed.

The cause of the degeneration and subsequent atrophy is obscure, just as it is obscure and entirely unknown in many other degenerative disorders (amyotrophic lateral sclerosis, multiple sclerosis and similar conditions). In one of the cases here recorded the atrophy and sclerosis

19. Taft, A. E., and Morse, M. E.: Hemiatrophy of the Cerebellum in a Case of Late Catatonia, J. Nerv. & Ment. Dis. **41**:553, 1914.

20. Pollak, Eugen: Zur Histologie und Pathogenese der Kleinhirnsklerose, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **21**:345, 1916.

21. Baird, Harvey: A Case of Sclerosis of the Cerebellum, J. Ment. Sc. **53**: 626, 1907.

were associated with leukemia and in another with dementia praecox. In an obscure case of Guillain and Bertrand's [22] cerebellar sclerosis of the quadrilateral lobe and vermis was associated with foci of degeneration, necrotic nodules in the motor area of the cerebral cortex and middle cerebellar peduncles. It has also been described in epilepsy, pernicious anemia, carbon monoxide poisoning, typhus fever and alcoholism (Stender and Lüthy [23])—in short, in a number of toxic infectious states. Scherer [24] mentioned at least thirty pathologic conditions in which features of cerebellar cortical atrophy have been described.

Grünthal [25] observed this condition in two cases of Paget's disease. He pointed out that in his cases only the portions of the cerebellum which were subject to pressure by thickened or deformed bones of the base (this showed an upward convexity) exhibited islands of sclerosis. According to Grünthal, the deformed clivus Blumenbachii and the protrusion of the sausage-like, thickened margins of the foramen magnum produced flattening of the cranial cavities which in their turn affected the configuration of the cerebellum and the brain. In the parts of the brain which were compressed the Purkinje cells were changed, the degree of the cell changes being in proportion to the extent of the pressure. Probably the mechanical factor was also essential in other cases of cerebellar cortical atrophy which have been recorded. In this connection attention should be called to the remarkable fact that in this morbid condition the upper or anterior surface of the cerebellum is mainly affected, especially the quadrilateral lobe and often the superior vermis, at any rate much more commonly than the inferior surface (Mathieu and Bertrand [26]). The reason for this is probably the fact that the upper cerebellar surface is exposed to pressure by the tentorium or the bulk of the overlying brain itself, while the base of the cerebellum is protected by the large cisterns. If such an etiologic factor is to be considered, problematic as it is, patches of sclerosis should be a rather common occurrence in the cerebellum. As they may give no clinical signs and develop slowly, they may escape detection, especially when they are small or involve only the Purkinje cells of the lateral hemis-

22. Guillain, G., and Bertrand, I.: Sur un type anatomo-clinique spécial d'atrophie cérébrale et cérébelleuse subaiguë avec foyers nécrotiques disséminés, Rev. neurol. **1**:577, 1929.

23. Stender, A., and Lüthy, F.: Ueber Spätatrophie der Kleinhirnrinde bei chronischem Alcoholismus, Deutsche Ztschr. f. Nervenh. **117-119**:604, 1931.

24. Scherer, Hans-Joachim: Beiträge zur pathologischen Anatomie des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:559, 1931.

25. Grünthal, E.: Ueber den Hirnbefund bei Pagetscher Krankheit des Schädels: Zugleich ein Beitrag zur Kenntnis der Entstehung systematischer Kleinhirnatrophien, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:656, 1931.

26. Mathieu, P., and Bertrand, I.: Etudes anatomo-cliniques sur les atrophies cérébelleuses, Rev. neurol. **1**:721 (May) 1929.

pheres (neocerebellum). When the vermis or paleocerebellum is affected, a clinical picture may be produced which is considered typical by Marie, Foix and Alajouanine. According to these investigators, late cerebellar atrophy may be suspected in elderly persons (50 years) in the presence of disturbances of equilibrium, asynergy and incoordination if intracranial hypertension is absent. If one takes into consideration the fact that cerebellar atrophy may occur in various toxic infectious states, a diagnosis may be exceedingly difficult or impossible.

The localizing value of the lesions occurring in cerebellar atrophy is not great. Often it is nil, for the lesions are usually scattered, affect only parts of a cerebellar lobe and frequently exhibit no clinical manifestations. For instance, though the lesions in the two cases reported here were extensive and could be recognized even grossly, the clinical records showed nothing that would even suggest a cerebellar involvement. Were the lesions described productive of localizing phenomena, some disturbances would have been manifest in the extremities—those of flexion, for instance, in analogy to the findings in experimental animals.[27] Probably acute lesions involving extensive areas and not mere patches are more prone to give rise to clinical manifestations, as is so well demonstrable in experiments on animals. Chronic, slowly developing patches of sclerosis ultimately resulting in cerebellar atrophy are often accidental findings and for this reason are of no clinical value. The cases of Lannois and Paviot,[7] Brouwer,[17] Huber [8] (cases 1 and 3) and especially Neubürger and Edinger [28] support such a view. In Neubürger and Edinger's case, for instance, the right cerebellar lobe was reduced to the size of a walnut and resembled the cerebellum of a 4 month fetus. On the other hand, as has been pointed out, the absence of Purkinje cells alone may give rise to severe clinical symptoms, and even here the extent of the cellular lesion does not always correspond with the wealth of the clinical picture. Mild lesions, especially in advanced age, may cause severe cerebellar symptoms and vice versa; this is explained by Vogt and Astwazaturow as a compensatory phenomenon.

CONCLUSIONS

1. Atrophy of the cerebellum may be an acquired morbid condition and in long-standing cases may result in sclerosis of parts of the cerebellum (sclerotic atrophy).

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27. Mills, C. K., and Weisenburg, T.: Cerebellar Symptoms and Cerebellar Localization, J. A. M. A. **63**:1813 (Nov. 21) 1914.

28. Neubürger, T., and Edinger, L.: Einseitiger fast totaler Mangel des Cerebellum; Varix oblongatae; Herztod durch Accessoriusreizung, Berl. klin. Wchnschr. **35**:69, 1898.

2. The lateral lobes, especially the upper semilunar and the quadrilateral, may alone be involved, or they may be affected together with the vermis.

3. Histologically, the condition somewhat resembles that occurring in any other terminal degenerative state when the nerve tissue is replaced by a glial tissue scar.

4. The cerebellar atrophy resulting from sclerosis has its homolog in the cerebral atrophy and sclerosis known as Pick's disease and possesses no specific histologic features.

5. The striking pathologic feature is calcification of the Purkinje cells in the areas that are undergoing atrophy.

6. The clinical features cannot be considered specific, and as they may be absent altogether, a pathologic condition of this sort remains undiagnosed.

CONTAMINATION OF THE CEREBROSPINAL FLUID BY BLOOD

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Examination of the cerebrospinal fluid is frequently a crucial point in diagnosis. If a "bloody tap" is encountered, however, the fluid is usually discarded as valueless. The resultant delay in diagnosis is always disturbing and may become a serious matter in the presence of an acute illness.

Bauckus and Foord,[1] Lange [2] and, more recently, Gordon [3] stated that even small quantities of blood vitiate the value of the examination of the cerebrospinal fluid. Levinson [4] advised waiting three days before repeating a puncture when traumatic blood is present. The literature, moreover, gives few quantitative data concerning the effect of contaminating blood on the composition of the cerebrospinal fluid.

It has been our experience over a period of years that much valuable information can be obtained from examination of a bloody spinal fluid, provided certain precautions are observed. In most instances sufficiently accurate information can be obtained from a bloody tap to serve the purpose for which the lumbar puncture was performed.

CRITERIA OF BLOODY TAP

The distinction between a bloody tap and previous subarachnoid hemorrhage is of first importance. Much has been written on the subject.[5] Gross variations in

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1. Bauckus, M., and Foord, A. G.: J. Lab. & Clin. Med. **13**:270 (Dec.) 1927.

2. Lange, C.: Infektionskrankheiten, Berlin, Urban & Schwarzenberg, 1923, vol. 2, pt. 3.

3. Gordon, J.: Diagnosis of Early Poliomyelitis, J. A. M. A. **99**:1043 (Sept. 24) 1932.

4. Levinson, A.: Cerebrospinal Fluid in Health and Disease, ed. 3, St. Louis C. V. Mosby Company, 1929, p. 229.

5. (*a*) Quincke, H.: Berl. klin. Wchnschr. **38**:927 and 965, 1891. (*b*) Jacoby, G.: New York M. J. **62**:813, 1895; **63**:6, 1896. (*c*) Furbringer: Berl. klin. Wchnschr. **32**:272 and 287, 1895. (*d*) Stadelmann, E.: Deutsche med. Wchnschr. **47**:745, 1897. (*e*) Netter: Semana méd. **18**:281, 1898. (*f*) Henneberg: Centralbl.

(*Footnote continued on following page*)

the amount of blood in successive tubes of fluid, the presence of a clot and a colorless supernatant fluid after centrifugation distinguish the fresh bleeding of a bloody tap from that of previous subarachnoid hemorrhage. In the latter the blood tends to be evenly distributed in all tubes of fluid collected; clotting is absent, and the supernatant fluid is xanthochromic (provided the hemorrhage did not occur within three hours of the lumbar puncture). Table 1 illustrates these distinctions.

In fresh bleeding, variations in the amount of blood in succeeding tubes can sometimes be accentuated by varying the rate of flow. It is always advisable to obtain separate specimens of fluid in three or more tubes and to compare the amount of blood in the different tubes. In most bloody taps the difference is striking. Very rarely does the bleeding caused by trauma due to a needle produce a uniform admixture of blood, while occasionally in subarachnoid hemorrhage the fluid becomes progressively less bloody.

Xanthochromia begins to appear within a few hours following subarachnoid bleeding and increases steadily for several days. It may at first be so slight that a comparison of the supernatant fluid with water in a test tube of similar size is necessary to detect it. In rare cases such gross bleeding (more than 100,000 red blood cells per cubic millimeter may be produced by the needle that the amount

TABLE 1.—*Distinctions Between the Fluid in a Bloody Tap and in Subarachnoid Hemorrhage*

Bloody Tap	Subarachnoid Hemorrhage
1. Gross variations in amount of blood in successive tubes	1. Relatively even admixture of blood
2. Clot present*	2. Clot absent
3. Colorless supernatant fluid	3. Supernatant fluid xanthochromic

* Very small amounts of fresh blood may be present without clot.

of serum entering the cerebrospinal fluid with the red cells is enough to color the supernatant fluid. With severe or prolonged jaundice the cerebrospinal fluid may become xanthochromic. We found that xanthochromia due to jaundice disappears in a few minutes if exposed to direct sunlight, whereas the color due to subarachnoid hemorrhage is not appreciably affected. Schlack [5x] made similar observations in cases of icterus neonatorum.

f. Nervenh. **11**:8, 1900. (*g*) Bard, L.: Compt. rend. Soc. de biol. **103**:747, 1901. (*h*) Sicard, J.: ibid. p. 1050; (*i*) ibid. p. 1049. (*j*) Tuffier, T., and Milian G.: Presse méd. **10**:221, 1902. (*k*) Brumeau, A.: Marseille-méd. **39**:236, 1902. (*l*) Tuffier, T., and Milian, G.: Bull. et mém. Soc. anat. de Paris **77**:489 (May) 1902. (*m*) Gilbert and Castaigne: Compt. rend. Soc. de biol. **102**:877, 1900. (*n*) Bard, L: Semaine méd. **23**:333, 1903. (*o*) Froin: Gaz. d. hôp. **73**:1257 (Nov. 5) 1903. (*p*) Bard, L.: Semaine méd. **23**:9, 1903. (*q*) Sabrazes, J., and Muratet, L.: Compt. rend. Acad. d. sc. **55**:1435, 1903. (*r*) Gerhardt, D.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:501, 1904. (*s*) Hérault, M.: Contribution à l'étude de la ponction lombaire dans les hémorragies du névraxe, Thèse de Paris, 1905, no. 508. (*t*) Ohm, J.: Deutsche med. Wchnschr. **42**:1694, 1906. (*u*) Schwartz, E.: Deutsche Ztschr. f. Chir. **124**:346, 1913. (*v*) Leschke, E.: Deutsche med. Wchnschr. **47**:376, 1921. (*w*) Raue, F.: Klin. Wchnschr. **6**:265, 1925. (*x*) Schlack, H.: München. med. Wchnschr. **75**:1502, 1928. (*y*) Eskuchen, K.: Lumbalpunktion, Berlin, Urban & Schwarzenberg, 1919, p. 78. (*z*) Symonds, C. P.: Quart. J. Med. **18**:93, 1924.

If a clot forms in the bloody fluid, the blood is fresh. The clot may be small, resembling a pellicle, and if there is little blood it may not form immediately, but it is never found if the subarachnoid bleeding occurred previous to the lumbar puncture, unless other conditions, such as meningitis or a superimposed bloody tap, are present to produce it.

If, then, a fluid is seen to be bloody when it starts to flow from the needle, but becomes much less bloody as it continues to flow, if it clots and if on centrifugation the supernatant fluid is found to be colorless, one is dealing with a bloody tap. Occasionally the fluid may be clear at first and afterward become bloody.

CELL COUNT

Wüllenweber [6] believed that pleocytosis could be recognized in spite of a slight amount of contaminating blood. Pappenheim [7] assumed the usual proportion of red cells to white cells in the blood to be 600:1; he used this ratio to determine the number of white cells which could be accounted for in the cerebrospinal fluid as having entered with the red cells. He admitted that this is not accurate. Steiner [8] used Pappenheim's method in the diagnosis of meningitis in children, but thought that the method was subject to considerable error and useful only when the white cells were definitely increased. He also made a differential count on a stained smear (a procedure which Pappenheim had also recommended), since in tuberculous meningitis one expects to find mostly lymphocytes and in purulent meningitis, polymorphonuclear leukocytes. Samson [9] said that theoretically it would be advisable to make a red cell and white cell count on the patient's peripheral blood and use the ratio so obtained to calculate the cell count in the original uncontaminated cerebrospinal fluid. He believed that it is within the limits of error of the method, if the patient does not have a leukocytosis, to assign one or two white cells for every 1,000 red cells.

The assumption that 1 white blood cell enters the cerebrospinal fluid with every 500 red blood cells (approximately the values used by Pappenheim and Samson) is sufficiently accurate in most cases. In patients with fever, when the white cell count is high, or with anemia, when the red cell count is low, this assumption may lead to results unnecessarily erroneous. For greater accuracy, red and white cell counts should be made for the patient's blood immediately after the lumbar puncture. The least bloody specimen of cerebrospinal fluid is used for an accurate count of the red and white cells. If RBC_B and WBC_B represent the cell counts in the blood, RBC_F and WBC_F the cell counts in the cerebrospinal fluid and W the white cells originally in the fluid,

$$(1)\quad W = WBC_F - \left[\frac{WBC_B}{RBC_B} \times RBC_F\right]$$

To determine the accuracy of this method, the following experiments were carried out: Normal cerebrospinal fluid containing no cells was diluted with

6. Wüllenweber, G.: Klin. Wchnschr. **3**:1756, 1924.

7. Pappenheim, M.: Lumbar Puncture, New York, William Wood & Company, 1923.

8. Steiner, B.: Orvosi hetil. **70**:487, 1926.

9. Samson, K.: Klin. Wchnschr. **8**:971, 1929.

varying amounts of venous blood from a normal subject for whom a red and white cell count had just been made. These mixtures were then treated in the manner recommended.

Table 2 shows the close agreement between the observed white cell count, that calculated by equation 1 and that obtained using the ratio 1 WBC: 500 RBC.

PROTEIN CONTENT

It was recognized early that tests for increased globulin in the cerebrospinal fluid were not reliable in the presence of an admixture of blood. Levinson [4] stated that in performing a globulin test one must make sure at the beginning that the fluid is perfectly free from blood; if there should be blood in the fluid, the globulin test will be positive

TABLE 2.—*Comparison Between Observed and Calculated White Cell Counts in Cerebrospinal Fluid Experimentally Contaminated with Varying Amounts of Blood*

Added Red Blood Cells, per C.Mm.	White Blood Cells Counted, per C.Mm.	White Blood Cells Calculated by Equation 1, per C.Mm.	White Blood Cells Calculated by Ratio, 1 WBC : 500 RBC, per C.Mm.
(11/4/32: Red blood cells, 5,000,000 per c.mm.; white blood cells, 11,450 per c.mm.)			
0	0	0	0
1,040	3	2	2
1,960	4	4	4
3,590	6	8	7
7,400	13	17	15
(11/4/32: Red blood cells, 4,500,000 per c.mm.; white blood cells, 10,700 per c.mm.)			
0	0	0	0
25	0	0	0
1,320	3	3	3
3,160	7	8	6
5,110	13	12	10
9,160	24	22	18
20,250	46	48	41
35,120	64	83	70
45,000	113	107	90
146,000*	340	347	292
272,000*	633	646	544

* Glacial acetic acid was used when the cells were counted.

even if no pathologic process exists. Feinberg,[10] in 1921, thought that this statement was too sweeping. He found that the Ross-Jones test was negative unless there were 300 or more red cells per cubic millimeter in the fluid. He concluded that a positive test in the presence of less than 300 red cells per cubic millimeter was significant. He was the first to advocate an actual count of the number of red blood cells present. Wüllenweber [6] investigated the Nonne, Pandy and Weichbrodt tests in a similar manner and found that in bloody fluids they were "too sensitive," since "with only a little blood" they became positive and were likely to be misleading. Steiner,[8] who did not offer experimental evidence, was of the opinion that the Pandy test was too sensitive to use for bloody fluids, while the Nonne-Apelt test could be used with caution. Teschler [11] found that the Nonne-Apelt reaction

10. Feinberg, S.: J. Lab. & Clin. Med. **6**:642, 1921.
11. Teschler, L.: Deutsche Ztschr. f. Nervenh. **98**:274, 1927.

was positive in the presence of from 600 to 800 red cells per cubic millimeter. Samson [9] made a table showing the amount of serum protein which entered the cerebrospinal fluid with varying amounts of blood. By counting the cells in the fluid, the amount of contaminating serum protein due to the bleeding could be estimated and subtracted from the total protein to obtain the original protein content of the cerebrospinal fluid. Lange's [2] more complicated method involved a colorimetric estimation of hemoglobin after the red cells had been laked to determine the amount of contaminating blood and serum protein.

Fremont-Smith and Hodgson [12] showed the value of comparing the protein contents of fluids from the lateral ventricles in localizing tumors of the brain. Since fluid obtained by ventricular puncture often contains contaminating blood and since normal ventricular fluid may contain even less than 5 mg. of protein per hundred cubic centimeters, the accuracy with which the protein can be determined assumes considerable importance.

The original protein content (P) may be calculated with the greatest accuracy if the patient's red blood cell count (RBC_B), serum protein (P_B) and hematocrit value of the blood (H) are known. P_F represents the protein content of the fluid as determined, and RBC_F the red count in the fluid.

$$(2)\quad P = P_F - \left[\frac{RBC_F}{RBC_B} \times P_B\,(1 - H)\right]$$

The error caused by assuming an average serum protein of 7 per cent [13] and a hematocrit reading of 43 per cent [14] is practically negligible. Serum protein and hematocrit values need not be determined unless there is reason to believe they are definitely abnormal.

A further simplification may be made by assuming a red cell count of 5,100,000.[14a] Equation 2 then becomes:

$$(3)\quad P = P_F - 0.0008\,RBC_F$$

In other words, unless the patient is very anemic, the original protein can be estimated with sufficient accuracy by subtracting from the determined protein 4 mg. per hundred cubic centimeters for each 5,000 red cells. Experiments were arranged to check equation 2. Serum protein and hematocrit values were determined on a sample of blood, which was added in varying amounts to the cerebrospinal fluid. Determinations for protein were then made on the original cerebrospinal fluid and on the various dilutions with blood after centrifugation.

It can be seen in table 3 that with the exception of the specimen which contained the most blood, the agreement of observed and calculated values is very close.

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12. Fremont-Smith, F., and Hodgson, J. S.: The Human Cerebrospinal Fluid, New York, Paul B. Hoeber, Inc., 1926, chap. 12.

13. Fremont-Smith, F., and others: Equilibrium Between Cerebrospinal Fluid and Blood Plasma. Composition of Human Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1271 (June) 1931.

14. (*a*) Osgood, E.: J. Lab. & Clin. Med. **12**:899, 1927. (*b*) Wintrobe, M.: ibid. **15**:287, 1929.

In the preceding discussion it was assumed that the cerebrospinal fluid was centrifugated before hemolysis of the red cells took place, and that consequently the supernatant fluid was colorless. If one finds that the supernatant fluid is colored, indicating hemolysis, the equations given for the determinations of the protein will be inaccurate. The amount of additional protein added by the hemolyzed red cells and the serum that entered with them can be estimated roughly from the color of the supernatant fluid. To determine experimentally the relation between

TABLE 3.—*A Comparison Between the Observed and Calculated Protein Content of the Cerebrospinal Fluid Experimentally Contaminated with Varying Amounts of Blood* *

Added Red Blood Cells per C.Mm.	Determined Protein, Mg. per 100 Cc.	Original Protein, Mg. per 100 Cc.	Original Protein by Equation 2, Mg. per 100 Cc.	Original Protein by Equation 3, Mg. per 100 Cc.
25	38	38	38	38
1,320	38	38	37	37
3,160	38	38	36	36
5,110	40	38	38	36
9,160	43	38	37	36
20,250	55	38	40	39
35,120	68	38	42	40
45,000	69	38	36	33
146,000	147	38	40	30
272,000	270	38	70	52

* The blood used in this experiment had 4,500,000 red blood cells per cubic millimeter, and 10,700 white cells per cubic millimeter. The hematocrit value was 43 per cent; the serum protein, 5.8 per cent.

TABLE 4.—*Increase in Protein and in Color Caused by the Hemolysis of Varying Amounts of Blood in Cerebrospinal Fluid*

(Original protein = 33 mg. per hundred cubic centimeters)

Approximate Red Blood Cells per C.Mm.	Determined Protein, Mg. per 100 Cc.	Actual Increase, Mg. per 100 Cc.	Calculated Increase, Mg. per 100 Cc.	Color
Saponin (control)	0	0	0	Colorless
125	33	0	0	Colorless
250	33	0	0	Colorless
500	33	0	1	Colorless
1,000	35	2	3	Slight pinkish yellow
2,000	41	8	7	Definite but slight yellow
4,000	53	20	14	Very light yellow
8,000	70	37	28	Light yellow
16,000	89	56	55	Slight pinkish-yellow
32,000	174	141	110	Light salmon pink
64,000	294	261	221	Pale yellowish-red
128,000	570	537	442	Yellowish-red
256,000	774	741	883	Intense yellowish-red

the amount of protein added and the color we hemolyzed various mixtures of cerebrospinal fluid and blood by the addition of saponin and recorded the color and the protein content. It is important to use test tubes of uniform size. The inside diameter of our tubes measured 2.1 cm. In these tubes the smallest amount of blood which when hemolyzed caused a visible color corresponds to a count in the cerebrospinal fluid of 1,000 red blood cells per cubic millimeter. This caused an increase in protein of 2 mg. Hemolysis so slight as to cause no coloring of the supernatant fluid can be neglected. With further hemolysis the protein mounts rapidly. Table 4 gives the results of a series of determinations, red cell counts being calculated from the known dilution on the basis of the red cell count in the blood. It can be seen that when much hemolysis occurred considerable error

was introduced. Every effort should be made to avoid hemolysis. Test tubes should be dry-sterilized. Stoppers, needles and manometers should be shaken as dry as possible after sterilization. Bloody fluid should be centrifugated as soon as possible and the supernatant fluid removed at once. Centrifugation should be done at medium speeds and for a period of a few minutes only. If these precautions are taken hemolysis should be at a minimum.

We measured various known amounts of blood into tubes containing tenth-normal hydrochloric acid, dilutions being made to correspond to red cell counts of from 25,000 to 250,000. The protein values of the solutions were calculated on the basis of an average red cell count of 5,100,000 and a protein value for whole blood of 18,000 mg. per hundred cubic centimeters.[15] One cubic centimeter of each of these dilutions was put in a series of tubes of uniform size and used as standard for comparison with fluids in which the amount of hemolysis was unknown. The acid hematin gave a color which was constant and could be used for comparisons. To 1 cc. of the centrifugated cerebrospinal fluid in which there had been hemolysis, 1 drop of normal hydrochloric acid was added and the color was compared with the standards, a tube of the same size being used. When the amount of protein corresponding to the hemolysis was estimated, the value was subtracted from the value determined by equation 3 to obtain the original protein content of the cerebrospinal fluid.

SUGAR DETERMINATIONS

In the absence of meningitis the cerebrospinal fluid sugar varies with the blood sugar. The usually accepted normal values during fasting[13] were from 50 to 75 mg. per hundred cubic centimeters for the cerebrospinal fluid as against from 70 to 110 for the blood, the former being in most cases about 65 per cent of the latter. When normal values are to be expected, therefore, even large contaminations can be neglected. In meningitis a moderately low spinal fluid sugar might conceivably be masked by contamination with a large amount of blood. For example, a spinal fluid sugar of 40 mg. per cent could be raised to 50 by a 17 per cent admixture of blood with a sugar content of 100 mg. This would mean a bloody fluid with a red cell count of over 800,000, more than is usually seen in grossly bloody fluids. Bloody fluids with a red cell count of 100,000 per cubic millimeter could give a sugar value at the most of only 3 mg. above the original value.

Theoretically, contaminating blood due to trauma from a needle can usually be disregarded as far as the sugar determination is concerned. Steiner,[8] in discussing this question, argued in a similar vein. He concluded that while ordinarily a diagnosis of meningitis can be made when the sugar value is below 50 mg. and can be excluded when the sugar content is above 55 mg., in bloody fluids due to trauma from a needle these limits must be widened to below 50 and above 65 mg.

In a doubtful case the amount of error due to contamination by blood can be determined by counting the red cells in the cerebrospinal

15. Mathews, A. P.: Physiological Chemistry, ed. 5, New York, William Wood & Company, 1930, p. 477.

fluid. If the count is less than 10 per cent of the red cell count of the blood, it can be disregarded. If it is more than 10 per cent, the amount of sugar added to the fluid can be calculated by direct proportion when the red blood cell count and the blood sugar values are known.

Since blood often contains glycolytic ferments not present in the cerebrospinal fluid, care must be taken in preserving a bloody fluid for sugar determinations. If the test cannot be made at once, a crystal of thymol should be added which will prevent glycolysis for at least twenty-four hours.

CHLORIDE DETERMINATIONS

The usually accepted normal values for the cerebrospinal fluid chlorides are from 710 to 750 mg. per hundred cubic centimeters expressed as sodium chloride, whereas serum chlorides are from 570 to 620.[13] A normal chloride value for spinal fluid might appear slightly low, owing to gross contamination with blood. However, to lower a chloride value of 710 to 680 would require 20 per cent admixture with blood, corresponding to a spinal fluid with 1,000,000 red blood cells per cubic millimeter; 100,000 red blood cells would make a difference of only 3 mg. per hundred cubic centimeters. Changes in the spinal fluid chlorides due to contamination with blood can be neglected for all practical purposes. In borderline cases in which the fluid is grossly bloody, the approximate error due to the blood can be estimated if the red cell count of the spinal fluid is known.

COLLOIDAL REACTIONS

Wüllenweber [6] was the first to recognize that the colloidal reactions in cerebrospinal fluid are not valueless in the presence of contaminating blood. He offered a table in which the mastic curves are given for the centrifugated fluid after dilution with three different amounts of blood. These were compared with curves obtained by adding the same amount of blood to fluids in cases of dementia paralytica. There was no difficulty in distinguishing normal fluids from those in cases of dementia paralytica under these circumstances. Wüllenweber believed that if too much blood is added the distinction cannot be made. In 1928, Mehrtens and his associates [16] studied the colloidal gold reaction in fluids experimentally contaminated with serum, washed red cells and whole blood. He found that serum (in amounts corresponding to a red cell count of 25,000 per cubic millimeter) produced a rise, chiefly in the center of the curve, to a height of 3 or 4, while washed red cells or whole blood produced the typical curves of dementia paralytica, except

16. Mehrtens, H. G.; Wyckoff, H. A., and Davis, R. M.: Colloidal Gold Reactions with Spinal Fluid Contaminated with Blood, Arch. Neurol. & Psychiat. **19**:296 (Feb.) 1928.

that the most marked precipitation did not occur in the first two tubes. The fluids from cases of dementia paralytica were not affected by these contaminants, while the meningeal fluids showed a somewhat exaggerated curve, difficult to distinguish from a contaminated normal fluid. It was shown that the length of time the contaminants were allowed to remain in the fluid had no influence on the result unless hemolysis occurred, in which case a curve like that in cases of dementia paralytica was produced. This effect was demonstrated to be due to hemoglobin, since it could be produced by adding hemoglobin alone, while adding the washed stroma of red cells caused no change in the curve.

The only other work we have been able to find in the literature on this subject is that of Samson [9] who elaborated on Wüllenweber's treatment of the mastic curve. Samson showed that there is no change in the mastic curve unless more than 24,000 red cells per cubic millimeter

TABLE 5.—*Effect of Contamination with Blood on Colloidal Reactions*

	Added Red Blood Cells per C.Mm.	Colloidal Gold Reaction	Mastic Reaction
Case A	0	0000000000	0000000000
	120	0000000000	0000000000
	950	0000000000	0000000000
	1,350	0000000000	0000000000
	5,500	0011110000	0000000000
	6,000	0121100000	0000000000
	10,000	0112100000	0000000000
	14,800	0111210000	1100000000
	24,100	0111210000	1110000000
	25,000	0112211000	0111000000

are added to the cerebrospinal fluid. The test was performed with centrifugated fluid. Even with large quantities of blood a strong reaction was never obtained. His conclusions agree with Mehrtens' contention that pathologic and normal curves are merely exaggerated by the addition of blood serum and are not changed in character. De Thurzo [17] remarked that small amounts of contaminating blood do not affect the bicolored mastic reaction.

We obtained simultaneous colloidal gold and bicolored mastic reactions [18] on fluids experimentally contaminated with varying amounts of blood. After centrifugation the supernatant fluid was used in each case, and every effort was made to avoid hemolysis. The results are shown in table 5. It can be seen that the colloidal gold reaction is more sensitive to changes produced by blood than the mastic reaction, as the former becomes definitely abnormal with as few as 6,000 red cells, while the

17. de Thurzo, E.: Les nouvelles méthodes sur les réactions colloïdales du liquide céphalo-rachidien, Paris, N. Maloine, 1927.

18. The bicolored mastic reactions were obtained for us by Dr. Eugene de Thurzo.

latter does not become abnormal with the addition of 25,000 red cells. However, if the changes shown in table 5 are considered in evaluating the colloidal gold test, results of practically equal value can be obtained. In an unknown contaminated cerebrospinal fluid, changes greater than those shown in table 5 can be regarded as of pathologic significance if the fluid is centrifugated before the test is done and no hemolysis has occurred.

WASSERMANN REACTION

Teschler,[11] Wüllenweber,[6] Bauckus and Foord,[1] Kafka[19] and Stalder and Strehler[20] investigated the value of the Wassermann reaction in cerebrospinal fluid contaminated with blood. The work of Bauckus and Foord is well controlled. They showed that the readings obtained by testing negative fluid containing varying amounts of positive serum were essentially the same as those obtained by testing salt solution containing the same amounts of the serum. As little as 0.01 cc. of a positive serum in 2 cc. of cerebrospinal fluid or salt solution (equivalent to 50,000 red cells per cubic millimeter of cerebrospinal fluid) produced a slightly positive test, while 0.04 cc. was enough to produce a 4+ test. These investigators believed that the reaction depends entirely on the strength of the positive reaction in the blood and on the amount of dilution which takes place when it contaminates the cerebrospinal fluid. They concluded that while microscopic amounts of blood can be neglected as of no importance, cerebrospinal fluid contaminated with grossly visible amounts of blood should not be used for the Wassermann reaction, as a positive test could be due either to neurosyphilitic disease or to "positive" blood. They pointed out, however, that a negative reaction is as reliable as it is in fluid not containing blood. We believe that these conclusions are as accurate and justifiable as present knowledge allows.

COMMENT

If there is a considerable difference in the number of blood cells in the lumbar pial vessels and the peripheral veins, as Samson[9] suggested, it would invalidate exact quantitative methods. The literature assures us that the red cell count can be assumed to be approximately the same.[21] The literature on the white cell count is less conclusive,[22] but the variations are not such as to make our assumptions unjustifiable.

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19. Kafka, V.: Dermat. Wchnschr. **78**:23, 1924.

20. Stalder, W., and Strehler, W.: Schweiz. med. Wchnschr. **62**:752, 1932.

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Two opportunities to demonstrate the practicability of the methods advocated occurred during lumbar punctures at which the fluid, at first clear, became bloody after some had been removed and the needle had been manipulated. Contaminated fluid was then collected. Following the lumbar puncture, blood was taken from the patient for red and white cell counts and total protein and hematocrit determinations. The uncontaminated fluid and the contaminated specimen were examined, and the calculations suggested were used for determining from the bloody fluid the cell count and the protein content of the original fluid. A comparison of the original and the corrected results is shown in table 6.

TABLE 6.—*Comparison of Clear Cerebrospinal Fluid with the Same Fluid Contaminated with Blood; Results Obtained by Applying the Suggested Corrections*

Case A*	Blood	Bloody Cerebrospinal Fluid	Cerebrospinal Fluid Corrected for Contamination with Blood	Original Cerebrospinal Fluid
Red blood cells (per c.mm.)	4,080,000	34,200	..	0
White blood cells (per c.mm.)	6,700	64	8	2
Protein (mg. per 100 cc.)	6,100	58	29	21
Hematocrit (vol., per cent red blood cells)	43.5			
Colloidal gold reaction		0001210000		0001100000
Mastic reaction		1100000000		0000000000
Case B				
Red blood cells (per c.mm.)	4,760,000	10,680	..	0
White blood cells (per c.mm.)	9,700	20	6	4
Protein (mg. per 100 cc.)	6,400	54	46	40
Hematocrit (vol., per cent red blood cells)	42.0			
Colloidal gold reaction		1222321000		2233210000

* The Wassermann test of the blood in this case was positive in a 1:40 dilution; examination of the spinal fluid gave negative results. A bloody spinal fluid (containing approximately 500,000 red blood cells) in a 1:4 dilution gave a positive reaction. The diagnosis was tabes dorsalis (under treatment).

SUMMARY OF PRACTICAL METHOD

If the cerebrospinal fluid flowing from the lumbar puncture needle is seen to be bloody, one should determine whether or not the blood is due to trauma from the needle. A small amount of fluid should be collected in each of several tubes. If there is an obvious increase or decrease in the amount of blood contained in successive tubes, one is probably dealing with trauma due to the needle. If the change is not apparent, the rate of flow from the needle should be varied by turning the petcock slightly. Usually, in trauma due to the needle, slowing the rate of flow results in more blood in the fluid.

If the fluid clears as it flows, it should be collected in a series of tubes, as the last specimens are likely to be much less bloody than the

first. If the fluid is so grossly bloody that it flows only with difficulty and soon clots, it is wiser to remove the needle and repeat the puncture a space higher with a fresh needle.

The least bloody sample should be mixed thoroughly by gentle shaking, and a small portion of it should be poured off for the cell counts. The remainder should be centrifugated at medium speed. This should be done as soon as possible in order to avoid errors introduced by hemolysis. Examining the centrifugated specimen should corroborate the diagnosis of needle trauma. The supernatant fluid will be found to be colorless, even when compared with tap water, and the sediment will usually show some clot formation on standing. In subarachnoid hemorrhage the supernatant fluid begins to be xanthochromic within three or four hours after the bleeding, and formation of clot does not take place.

The next step in the procedure depends on the reason for which the lumbar puncture was done. In spite of the contamination with blood, information of value can be obtained regarding the cell count, the protein, sugar and chloride values and the colloidal gold and Wassermann reactions. In every case a careful red cell and white cell count should be made on the cerebrospinal fluid set aside for this purpose. In most cases both counts can be made together by staining with Unna's polychrome methylene blue, which stains the white cells blue and the red cells yellow. The stain is drawn up to the 0.5 mark in a pipet such as is used for counting white blood cells, and the fluid is drawn up to the 11 mark. This is shaken for one minute and counted. The result is multiplied by 20/19 to correct for dilution.

In cases of suspected meningitis, poliomyelitis, and encephalitis, or in cases in which the exact cell count is of especial importance, a white cell count should be made at once on the patient's blood. If there is reason to expect the red cell count to be abnormal, a red cell count should be made also. The number of white cells which entered the cerebrospinal fluid with the contaminating blood can then be calculated by direct proportion (equation 1). Smears should be made of the sediment from the centrifugated specimen and stained with Wright's stain for a differential count and with Gram's stain for organisms. A specimen of cerebrospinal fluid should be cultured. The sugar and chloride determinations should be made immediately on the supernatant fluid, since these are little affected by contaminating blood and are of considerable diagnostic value in questions of infection of the central nervous system.

When the presence of a tumor is suspected, the cell count should be corrected as before, but here the exact protein value is of chief importance. The protein determination is made on the supernatant fluid, and the value is corrected according to the number of red cells contaminating

the specimen, equation 3 being used. In comparing ventricular fluid proteins, more accuracy is needed; a red cell count should be made on the patient's blood, and equation 2 should be used. If for any reason the patient's blood protein or hematocrit values are thought to be abnormal, these can be determined and used in equation 2. If hemolysis has occurred in the supernatant cerebrospinal fluid, the protein value should be corrected by using table 4 or by comparing with a set of standards such as those previously described.

When the presence of syphilis is in question, the cell count and protein value should be ascertained and corrected. Part of the supernatant fluid should be submitted to a colloidal gold or mastic test and part to a Wassermann test. While slight changes may occur in the colloidal tests, owing to contaminating blood, these usually can be distinguished from the changes characteristic of syphilis of the central nervous system.

If the Wassermann test of the blood is positive, a positive reaction in contaminated cerebrospinal fluid is not of value, but a negative reaction is significant.

When the lumbar puncture is done for reasons other than those discussed, the procedures which should be carried out to correct for contamination are similar and can be easily arranged to suit the particular case. If not practicable to carry out the more exact procedures necessitating studies of the patient's blood, consideration of the following gives a good approximation: 1. The corrected white cell counts can be obtained by subtracting 1 white cell for every 500 red cells in the cerebrospinal fluid. 2. The corrected protein content can be obtained by subtracting 4 mg. per hundred cubic centimeters for every 5,000 red cells present. 3. The sugar and chloride values are usually not appreciably affected by contaminating blood. 4. The colloidal gold test is not affected unless the red cells number over 5,000, and the bicolored mastic test unless the red cells number over 25,000. 5. A negative Wassermann reaction in a bloody cerebrospinal fluid is reliable, but a positive Wassermann reaction in a bloody cerebrospinal fluid is significant only when the Wassermann reaction of the blood is negative.

CONCLUSION

Cerebrospinal fluid accidentally contaminated with blood can be of diagnostic value. A corrected cell count, protein, sugar and chloride determination and colloidal reaction can be obtained by the methods given. These results closely approximate the values in the cerebrospinal fluid before contamination with blood.

ACUTE LYMPHOCYTIC MENINGITIS

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Scant attention has been paid in America to a symptom-complex which has been widely discussed in Europe in recent years. Especially from France, Germany and Scandinavia have come reports of cases designated by various authors as acute benign idiopathic serous meningitis,[1] acute aseptic meningitis,[2] benign aseptic purulent meningitis,[3] and epidemic meningitis serosa.[4] Only recently have reports emanated from this country.[5]

In the syndrome to be discussed there is a prodromal period of one or two weeks, as a rule, during which the patient may have the symptoms of an infection of the upper respiratory tract. Then there is a sudden onset of headache, general malaise, vomiting, mild fever, a varying degree of rigidity of the neck and a mild Kernig sign. Signs in the pyramidal tract are unusual (Kecht [6]). Blurring of the disks is fairly common in adults. Rarely does involvement of the cranial nerves occur in these cases. The results of examination of the spinal fluid are distinctive of this syndrome; they are not in accordance with any of the described types of meningitis. There is an increase in the cell count, varying from a few hundred to a few thousand, with an almost exclusive lymphocytosis. Cultures and smears from the blood and spinal fluid give persistently negative results. The serologic reactions have been uniformly negative. As a rule the sugar content of the spinal fluid is normal, but it is often increased. The chlorides tend to be normal; the protein is slightly increased. The white blood cell count

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From the Neurologic Service of the Jewish Hospital.

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6. Kecht, B.: Zur Differentialdiagnose zwischen lymphocytärer Meningitis und multipler Sklerose, Klin. Wchnschr. **11**:1310, 1932.

is rarely above 10,000, even when there are more than 1,000 cells in the spinal fluid. The fever is seldom high or of long duration.

The course of the illness is relatively short—from one week to two months. The prognosis is good, no deaths having been reported from the disease per se (Knauer,[7] Eckstein[8]). Although some authors (Gibbens[9]) state that no sequelae result, a review of the literature indicates that this is not strictly true. The earlier cases occurred in children, but it is evident from later reports that the disease also affects young adults, males more often than females. Consciousness is rarely disturbed, though certain writers have reported the appearance of cerebral symptoms in varying degree.

Wallgren,[10] who regarded this type as a disease *sui generis,* characterized it as follows: (1) a sudden onset with meningeal signs and symptoms; (2) meningeal changes in the spinal fluid; (3) sterile fluid and negative cultures; (4) a relatively short course and benign character, with no secondary complications; (5) lack of a traceable etiology, such as trauma, infections of the ear, etc., and (6) lack of epidemiologic relations.

Several cases of this type have come under our observation in the past few years and are the basis for this report:

REPORT OF CASES

CASE 1.—H. M., a man, aged 20, who was admitted to the Jewish Hospital on Jan. 19, 1929, and discharged on Jan. 31, 1929, had become ill six days before with an infection of the upper respiratory tract and slight fever. A dry cough, headache and generalized aches were present. He had been progressing well until the night before admission when he collapsed in the bathroom.

Examination.—At the time of admission the patient was unconscious; the temperature was 104 F.; the pulse rate, 88; the respiratory rate, 22. He appeared acutely ill. The pupils were equal and round, and reacted well to light and in accommodation. There was no involvement of the cranial nerves. The biceps reflexes were active and normal. The knee jerks were not elicited. There was a bilateral Babinski sign but no ankle clonus. Marked rigidity of the neck was present, with only a mild Kernig sign. No Brudzinski sign was present.

Course.—A few hours after admission the patient was restless and the knee jerks were increased. On the next day the condition was worse, with more marked rigidity of the neck and a definite Kernig sign. However, following a spinal puncture the patient became conscious. Two days after admission the

7. Knauer, H.: Gehört die akute aseptische Meningitis zu den Encephalitiserkrankungen? Klin. Wchnschr. **11**:449, 1931.

8. Eckstein, A.; Hottinger, A., and Scheutzeng, H.: Ueber die Beziehungen der Meningitis serosa epidemica zur Poliomyelitis bzw. Encephalitis epidemica, Ztschr. f. klin. Med. **118**:98, 1931.

9. Gibbens, H.: Acute Aseptic Meningitis, Lancet **2**:12, 1931.

10. Wallgren, A.: Une nouvelle maladie infectieuse du système nerveux central, Acta pædiat. **4**:158, 1925.

temperature began to drop, and the patient improved. On January 26, serum sickness developed as the result of the administration of antimeningococcus serum, which had been given on January 19 when the spinal fluid was found to be turbid. At the time of discharge there were no neurologic signs. On January 19, the spinal fluid showed: 540 lymphocytes; Fehling's solution reduced; albumin, 1 mm. ring; globulin, 1 plus; sugar, 130 mg. per hundred cubic centimeters. On January 20, there were 1,280 lymphocytes in the spinal fluid. On January 28, there were 340 lymphocytes in the fluid and the sugar was 125 mg. All cultures were negative for tubercle bacilli. Inoculation of guinea-pigs gave negative results. All serologic reactions in the blood and spinal fluid were negative. The white cell count was 11,380, with 81 per cent polymorphonuclears and 18 per cent lymphocytes. On January 19, the spinal fluid was clear, but later in the day it became slightly turbid. Six hours later the fluid was clear again.

CASE 2.—H. P. a man, aged 35, who was admitted to the Jewish Hospital on Dec. 29, 1929, and discharged on Jan. 11, 1930, complained chiefly of headache for five days. He had vomited once. Two weeks before the onset of the illness he had had pains over the eyes, but no diplopia. The past history was unimportant.

Examination.—At the time of admission there were rigidity of the neck, a positive Kernig sign and no involvement of the cranial nerves. The fundi were normal; the knee jerks, lively; the abdominal reflexes were absent, and the Babinski sign was negative.

Course.—The abnormal findings gradually subsided, so that at the time of discharge, less than two weeks later, he did not have any symptoms. The temperature never rose above 100.5 F. On December 29, the spinal fluid showed 1,470 cells, 90 per cent of which were lymphocytes; Fehling's solution was not reduced; the albumin was 4 plus. On the next day there were 1,080 cells in the fluid, 98 per cent of which were lymphocytes; the sugar was 107 mg. per hundred cubic centimeters; the albumin was 3 plus. On January 7, there were 170 lymphocytes; the albumin was 3 plus, the globulin 4 plus and the sugar 47 mg. No tubercle bacilli were found. The urine was normal. The white cell count was 8,500, with 64 per cent polymorphonuclears and 28 per cent lymphocytes. All the cultures of the spinal fluid and blood and the serologic tests gave negative results.

CASE 3.—J. K., a woman, aged 22, who was admitted to the Jewish Hospital on July 15, 1930, and discharged on Aug. 29, 1930, complained chiefly of severe headache and malaise. She had gone swimming on July 5, and had experienced generalized malaise and headache that night. There had been occasional transient diplopia. She went to business for several days longer, but continued to complain of headache. The past history was irrelevant.

Examination.—The temperature was 101 F. The pupils were equal and round, and reacted well to light and in accommodation. There was blurring of the margins of the disks. All the deep reflexes were present. The cranial nerves were intact. The lungs and heart were normal. There was marked rigidity of the neck with a mild Kernig sign. The abdominal reflexes were not elicited. There was no Babinski or Brudzinski sign. Herpes was present on the genitalia and was beginning to ulcerate.

Course.—Four days later the patient had no symptoms, except for a slight headache. The temperature never went above 101 F. Roentgenograms of the chest were negative for tuberculosis. On the day of admission the spinal fluid contained 230 lymphocytes. Ten days later there were 130 lymphocytes, with 93 mg. of sugar per hundred cubic centimeters, and the reaction to the globulin

test was negative. On August 4, there were 40 lymphocytes; the sugar was 46 mg., the albumin 2 plus and the globulin 4 plus. On August 18, there were 60 lymphocytes; the sugar was 76 mg., the albumin 2 plus and the globulin 4 plus. No tubercle bacilli were found. All cultures and serologic tests gave negative results. The white cell count was 8,800, with 70 per cent polymorphonuclears and 24 per cent lymphocytes.

CASE 4.—R. M., a man, aged 33, who was admitted to the Jewish Hospital on Aug. 16 and discharged on Aug. 20, 1930, complained chiefly of inability to void urine, stiffness of the neck and headache. Two weeks before he had had a sore throat. He worked until two days before admission, when he suddenly lost sensation in the left arm. That evening he had a severe headache and stiffness of the neck developed. There were slight nausea and some vomiting. He said that he had not voided urine for two days. The past history was unessential.

Examination.—On admission, the temperature was 99.4 F. The pupils were equal and round, and reacted well to light and in accommodation. The fundi were normal. There were marked rigidity of the neck, a mild Kernig sign, no involvement of the cranial nerves and no Babinski sign. All the deep reflexes were present but diminished. The abdominal reflexes were not elicited. The heart and lungs were normal. All forms of sensation were intact.

Course.—The neurologic signs disappeared four days after admission. On the first day there were 450 lymphocytes in the spinal fluid; the albumin was 2 plus and the globulin 1 plus; Fehling's solution was reduced; the colloidal gold curve was normal. Nine days later there were 30 lymphocytes in the spinal fluid. There is no record of examination of the spinal fluid for the sugar content. All the serologic tests and studies of the blood gave entirely negative results. The white cell count was 8,200, with 67 per cent polymorphonuclears and 32 per cent lymphocytes. The highest temperature was 101 F.

CASE 5.—B. S., a woman, aged 38, who was admitted to the Jewish Hospital on Dec. 21, 1931, and discharged on Jan. 12, 1932, complained chiefly of headache and vomiting. She had been able to do her housework until two weeks before admission, when she was suddenly seized with a terrific occipital headache. She also became dizzy. That night she vomited. The headache and vomiting continued up to the time of admission. She said that during the illness at home she had a temperature of 104 F. In the past history it was noted that she had frequently vomited without apparent cause in the seventeen years of married life.

Examination.—On admission the temperature was 100.8 F. The pupils were in midposition, equal and round, and reacted well to light. The disks were blurred in outline; the vessels were full and tortuous, and there were many hemorrhages in the right eye. There was no involvement of the ocular muscles or cranial nerves. No rigidity of the neck was found. The knee jerks were active, but the abdominal reflexes were not elicited. There were no pathologic foot reflexes. Roentgen examination of the sinuses showed a possible pathologic condition of the left ethmoid and polypi in the right side of the nose. The sella turcica was normal.

Course.—The patient improved rapidly and left the hospital twenty-two days after admission. The highest temperature was 101 F. On December 23, there were 130 lymphocytes in the spinal fluid. On December 28, there were 400 lymphocytes; the sugar was 88 mg. per hundred cubic centimeters; the albumin and the

globulin were 2 plus. On January 4, there were 360 lymphocytes in the fluid; the sugar was 76 mg., the albumin 2 plus and the globulin 1 plus. Cultures of the blood and the serologic reactions were negative. The blood sugar was 115 mg. The white cell count was 9,200, with 46 per cent polymorphonuclears and 42 per cent lymphocytes.

CASE 6.—S. B., a woman, aged 30, who was admitted to the Jewish Hospital on March 21 and discharged April 12, 1933, complained chiefly of pain in the lower part of the back, mild epigastric distress, vomiting, loss of weight, increasing weakness and mild fever. These had begun three weeks before with pain across the lower part of the back, colicky in nature, but not radiating. The pain had no relation to meals or to exercise. The vomiting had begun four days before admission and was accompanied by occipital and parietal headaches, which were constant. In the past month she had lost much weight and there had been increasing weakness of the entire body. Just before admission she had suddenly become somnolent and had had twitchings of the body on the way to the hospital. The family and past history were without significance.

Examination.—At the time of admission the temperature was 100.4 F. At no time while the patient was in the hospital did the temperature rise above 100.8 F. There were a mild Kernig sign, with slight nuchal rigidity, which soon disappeared. The pupils were irregular and unequal, and reacted sluggishly to light. There was a mild drooping of the left corner of the mouth. There was no involvement of the muscles of the eye. Generalized hyperreflexia was present, but no pathologic foot reflexes were elicited. There was a systolic murmur at the apex of the heart. The lungs and sinuses were normal.

Course.—The patient showed marked improvement soon after admission, and at the time of discharge there was no evidence of involvement of the nervous system. A spinal tap on March 24 revealed clear fluid, under increased pressure, with 530 lymphocytes, 61 mg. of sugar per hundred cubic centimeters, albumin 1 plus and no globulin. The colloidal gold curve was normal; cultures of the blood and the Wassermann reaction were negative. On April 10, there were 10 lymphocytes; the fluid was under normal pressure; the sugar was 75 mg., and the chlorides were 710. The white cell count was 8,400, with 76 per cent polymorphonuclears and 28 per cent lymphocytes. The blood sugar was 102 mg. per hundred cubic centimeters of blood.

CASE 7.—Y. S., a woman, aged 40, who was admitted to the Jewish Hospital on May 9 and discharged on June 3, 1933, complained chiefly of lethargy and disorientation for eight hours. Three weeks before she had had a cough and had been told that she had the grip. She was intermittently in bed until just before admission, when lethargy, confusion and emotional instability developed. Ten days before she had had a subconjunctival hemorrhage of the left eye. In the past history it was noted that she had received treatment for an ulcerative colitis for the past five years. Recently she had been receiving stovarsol for this condition, with some improvement.

Examination.—At the time of admission the temperature was 101 F. The pupils were dilated and unequal, but reacted well to light and in accommodation. The disks were pale, with a large exudate temporal to the left disk. No rigidity of the neck was disclosed at this time. Babinski or Kernig signs were not present. All the deep reflexes were increased. The abdominal reflexes were not elicited.

Course.—Two days later there was nuchal rigidity, with a slight Kernig sign, and the knee jerks were increased. Three days later the rigidity of the neck was less. The temperature once rose to 103 F. but soon subsided. At the

TABLE 1.—*Summary of Observations* *

Case	Sex	Age	Month	Time in Hospital, Days	Rigidity of Neck	Kernig Sign	Babinski Sign	Involvement of Cranial Nerves	Highest Temperature, F.	White Cell Count
1	M	20	January	12	P	P	P	N	104	11,380
2	M	35	Dec.-Jan.	13	P	P	N	N	100.5	8,500 7,300
3	F	22	July-Aug.	44	P	P	N	N	101.0	8,800
4	M	33	August	4	P	P	N	N	101.0	8,200
5	F	38	Dec.-Jan.	22	N	N	N	N	101.0	9,200 9,100
6	F	30	March-April	21	P	P	N	P	100.8	8,400
7	F	40	May-June	24	P	P	N	P	103.0	14,000 8,000
8	M	19	Aug.-Sept.	26	P	P	N	N	104.0	12,000 7,900

* In this table P denotes positive and N negative findings on examination.

TABLE 2.—*Results of Examination of Spinal Fluid*

Case	Cells	Lymphocytes	Albumin	Globulin	Sugar, Mg. per 100 Cc.
1	540	All	1 plus	1 plus	130
	1,280	All	4 plus	4 plus	...
	340	All	.....	.....	125
2	1,470	90%	4 plus	.....	...
	1,080	98%	3 plus	Precipitate	107
	170	All	3 plus	4 plus	47
3	230	All	.....	.....	...
	130	All	1 plus	Negative	93
	40	All	.....	.....	46
	60	All	2 plus	4 plus	76
4	450	All	2 plus	1 plus	Not given
	30	All	.....	2 plus	
5	130	All	.....	.....	...
	400	All	2 plus	2 plus	88
	360	All	2 plus	1 plus	76
6	530	All	1 plus	Negative	61
	10	All	.....	.....	75
7	180	All	2 plus	Negative	...
	280	All	.....	.....	81
	210	All	4 plus	3 plus	71
	30	All	.....	.....	50
8	10	All	.....	.....	...
	46	All	Negative	Negative	4 plus
	560	All	Negative	Negative	4 plus
	8	...	.....	.....	...

time of discharge there were no neurologic signs. The colitis had improved. A spinal tap on May 9 showed: lymphocytes, 180; albumin, 2 plus; negative reaction to the globulin tests; cultures, sterile. On May 12, there were 280 lymphocytes and sugar was 81 mg. per hundred cubic centimeters. On May 16, a spinal tap revealed: lymphocytes, 210; sugar, 71 mg.; chlorides, 758; albumin, 4 plus;

globulin, 3 plus. On May 25, there were 30 lymphocytes and sugar was 50 mg. The white cell count was 14,000 at first and 8,000 three days later, with 64 per cent polymorphonuclears and 33 per cent lymphocytes. The blood sugar was 125 mg.

CASE 8.—P. L., a youth, aged 19, who was admitted to the Greenpoint Hospital on Aug. 11 and discharged on Sept. 6, 1931, complained chiefly of pain in the chest, night sweats, hemoptysis, chills and fever. The patient had had repeated colds in the past year. The family history was unimportant. Three days before admission the patient began to have chills, fever, severe pains in the chest and night sweats. He had coughed up blood several times during the day.

Examination.—At the time of admission the temperature was 101 F. The patient appeared acutely ill. Examination of the chest revealed evidence of tuberculosis; this was substantiated by the roentgen rays. Neurologic examination revealed that the pupils were equal and round, and reacted well to light; the fundi were normal; there was no involvement of the cranial nerves. There was slight rigidity of the neck with a mild bilateral Kernig sign. The patient was somewhat lethargic. The knee jerks and abdominal reflexes were active and equal. The Babinski sign was not elicited.

Course.—On the day following admission the patient complained of severe headache, but this was relieved after a spinal tap. On one occasion the temperature rose to 104 F., but it soon subsided. At the time of discharge the patient had no symptoms and there were no neurologic signs. On the day of admission there were 10 lymphocytes in the spinal fluid. On the next day there were 46 lymphocytes; the sugar was 4 plus; the reaction to the globulin test was negative. On August 18, there were 560 lymphocytes; the sugar was 4 plus; the reaction to the globulin test was negative. A week later there were 8 lymphocytes. On repeated examination no tubercle bacilli were found in the sputum or in the spinal fluid. All serologic reactions were negative. The blood sugar was 66 mg. per hundred cubic centimeters of blood. The white cell counts were 12,000, with 73 per cent polymorphonuclears and 18 per cent lymphocytes, and 7,900 with 81 per cent polymorphonuclears and 19 per cent lymphocytes.

COMMENT

The characteristic feature of the syndrome is the presence of a marked lymphocytosis in the spinal fluid. Numerous lymphocytes in a clear spinal fluid suggest anterior poliomyelitis, tuberculous meningitis, epidemic encephalitis and syphilis. It is true that herpes zoster, polyneuritis, multiple sclerosis, trypanosomiasis and cerebral abscess or tumor may occasionally give rise to from 10 to 30 lymphocytes in a clear spinal fluid. It is very rare for more than this number to appear in these diseases (Kecht). Only infrequently have over 100 lymphocytes been reported in cases of epidemic encephalitis (von Economo[11]). Poliomyelitis and tuberculous meningitis may give rise to a few hundred lymphocytes in a clear fluid (usually from 100 to 300, but occasionally

11. von Economo, C.: Encephalitis Lethargica, New York, Oxford University Press, 1931.

as high as 1,000[12]); Greenfield and Carmichael[13] stated that they personally had not encountered a case of extreme mononuclear pleocytosis, that is, one with more than 250 mononuclears per cubic millimeter. Rosenow[14] stated that in poliomyelitis:

> The cells are chiefly polymorphonuclear leukocytes in the cases in which spinal puncture was made on the first and second days of the disease; there were about equal numbers of these cells and lymphocytes in the fluid obtained on the fourth day of the illness, and a predominance of lymphocytes in those obtained in the fifth and seventh days.

This shift from polymorphonuclears to lymphocytes late in the disease is thought by some[15] to be pathognomonic of poliomyelitis. In the symptom-complex which has been described, however, this change in the type of cell has been rare, and the prominent feature has been a marked and almost exclusive lymphocytic pleocytosis in a clear fluid.

The etiology of the syndrome has given rise to a diversity of opinion and to confusion. The results of examination of the spinal fluid suggest the possibility of tuberculosis. Solomon[16] called attention to the fact that when cases of this type ended in recovery they were called "pseudotuberculous meningitis." Moreover, Etienne[17] and others[18] (Roch[19] in his first paper) believed that in many of their cases they were dealing with a tuberculous process, even though they were unable to demonstrate the tubercle bacilli by culture or by inoculation of guinea-pigs. This view, however, has not found favor with most authors.

Wallgren, Viets and Watts and others[20] were of the opinion that it is a disease *sui generis*. Strong evidence is accumulating, however, to refute this and to show its possible relationship to other diseases, especially to poliomyelitis and epidemic encephalitis.

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12. Strauss, I., and Kaliski, D. J.: The Human Cerebrospinal Fluid. An Investigation by the Association for Research in Nervous and Mental Diseases, New York, Paul B. Hoeber, Inc., 1924, vol. 4, p. 269.

13. Greenfield, J. G., and Carmichael, E. A.: Cerebrospinal Fluid in Clinical Diagnosis, New York, The Macmillan Company, 1925

14. Rosenow, E. C.: Poliomyelitis Antistreptococcus Serum, J. A. M. A. **94**:777 (March 15) 1930.

15. Campbell, G., and Mirsky, S.: Poliomyelitis: A Clinical Study, Canad. Pub. Health J. **21**:375, 1930. Lyon, G. M.: Cytolysis in the Cerebrospinal Fluid in Acute Poliomyelitis, Am. J. Dis. Child. **36**:40 (July) 1928.

16. Solomon, in discussion of Viets and Watts.[5a]

17. Etienne, G.; Verain, M., and Reny, J.: A propos de plusieurs cas de réactions meningées, à lymphoycytes, Rev. méd. de l'est **53**:160, 1924.

18. Cited in the bibliography of Gunther.[2a]

19. Roch, M.; Martin, E., and Mondjikova, V.: La méningite aigüe, lymphocytaire bénigne de nature indéterminée simulant la méningite tuberculeuse, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:402, 1930.

20. Quoted by Silberstein, J.: Meningitis linfocitarias benignas, Semana méd. **2**:1194, 1931.

The strongest advocate of the relationship of this type of disease to poliomyelitis is Gunther.[2a] He studied thirteen children who presented this syndrome in Gothenburg, Sweden. Most of the cases occurred in the fall months when there was an increased number of cases of poliomyelitis in the vicinity. Because of this fact and of the similarity of the clinical course of both diseases, Gunther favored the theory that poliomyelitis was the etiologic factor. He admitted, however, that a direct epidemiologic connection with typical cases of poliomyelitis has not been demonstrated in any instance. He concluded:

> It is possible that in certain of these cases we are dealing with abortive poliomyelitis—one must furthermore have doubts as to whether all cases were brought about by the virus of poliomyelitis. . . . The only positive conclusion that may be drawn from them is that the probability of a poliomyelitic etiology seems greater today than one was justified in assuming from earlier reports.

Eckstein [4] (in his first paper) also uttered the belief that this type of illness is an abortive form of poliomyelitis, but realized that it may possibly represent a form of epidemic encephalitis, especially since von Economo and others have described a meningeal form of epidemic encephalitis. Netter,[21] Antoni [22] and Lichtenstein,[23] among others, were further proponents of this relationship. Gibbens, on the other hand, argued against it on the following grounds: 1. In the epidemic which occurred in Paris in 1910 [24] there was no evidence of poliomyelitis in the vicinity. 2. No flaccid paralysis has ever occurred after this type of illness. 3. There is extraordinary uniformity of the symptoms in these cases, while in poliomyelitis the severity of the disease process varies from case to case.

Of late, many observers [25] have favored epidemic encephalitis as the etiologic factor in this syndrome. Of these, Roch [26] set forth the most convincing evidence in its favor. He based his opinion on the following evidence: (1) the polymorphism and the clinical transformation of epidemic encephalitis; (2) the numerous exceptions to the rule that

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21. Netter, quoted by Gunther.[2a]

22. Antoni, N.: Om hopade benigna meningiter under sensommar och höst (poliomyelitis acuta), Svenska läk.-sällsk. handl. **21**:321, 1924.

23. Lichtenstein, A.: Zur Kenntnis der gutartigen aseptischen eitrigen Meningitis, Deutsche med. Wchnschr. **57**:54, 1931.

24. Rist, E., and Rolland, I.: Méningites bénignes d'allure épidemique, Bull. et mém. Soc. méd. d. hôp. de Paris **2**:245, 1910. Laubry, C., and Parvu, M.: Syndrôme méningé avec lymphocytose rachidienne d'origine indéterminée, ibid. **2**:236, 1910.

25. Krabbe, K. H.: Benigne lymphocytaere meningiter, Bibliot. f. laeger **121**:511, 1929.

26. Roch, M.: Encore la méningite lymphocytaire bénigne. La forme méningée de l'encéphalite épidémique, Rev. méd. de la Suisse Rom. **51**:1, 1931.

epidemic encephalitis does not usually produce meningeal reactions; (3) the fact that cases of meningitis analogous to those reported by him have been attributable to encephalitis by reliable authors; (4) symptoms, such as a set appearance, catatonic attitudes and rhythmic myoclonias, which are indicative of epidemic encephalitis and which have been reported following this type of illness; (5) the report, in various cases, of symptoms of peripheral involvement analogous to peripheral forms of epidemic encephalitis.

In further support of this view is the fact that a follow-up of patients by some authors revealed the development of a parkinsonian syndrome. Gunther did not find this to be true in his series of cases; but Andersen and Wulff [1] reported this complication in two of their cases, Schneider [27] in one, Naucler [28] in one, Roch in two, and Eckstein in one. Gunther called attention to the fact that most authors have made no attempt to follow up their patients and determine the development of sequelae. Reexamination of six of our patients from one to two years after the illness revealed no neuropsychiatric disturbances.

In an effort to establish a possible relationship of this disease to epidemic encephalitis or to poliomyelitis Eckstein injected spinal fluid from three of his patients intraspinally into monkeys (Macacus rhesus). Only one animal became ill. Autopsy of this animal showed a meningomyelitis. Grün [29] repeated this work, but was unable to induce the disease in animals of this species. Of interest in this regard is the fact that several authors (Léri and Lièvre,[30] Turrettini and Choisy,[31] Grün and Roch) have reported the presence of herpes in their patients; the symptoms also occurred in one of our patients.

Thorp,[32] commenting on the cases reported by Rankin, concluded that no case of meningitis can be accepted the diagnosis of which rests solely on the results of lumbar puncture. From his work it is his contention that when no organisms have been found by spinal puncture, cisternal puncture is necessary, either post mortem or ante mortem. He found that by using these methods "aseptic meningitis becomes so

27. Schneider, H.: Ueber epidemische akute "Meningitis serosa," Wien. klin. Wchnschr. **1**:350, 1931.

28. Naucler, quoted by Wallgren.[10]

29. Grün, R.: Ueber benigne fieberhafte lymphocytäre Meningitis unbekannter Ätiologie, Deutsches Arch. f. klin. Med. **172**:429, 1932.

30. Léri, A., and Lièvre, J-A.: A propos des méningites aigües à lymphocytes non tuberculeuses. Sur un cas de méningite lymphocytaire passagère avec herpès, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:1256, 1930.

31. Turrettini, G., and Choisy, R.: Un cas de méningite lymphocytaire bénigne accompagnée d'herpès; guérison rapide après une ponction lombaire, Rev. méd. de la Suisse Rom. **51**:22, 1931.

32. Thorp, E., in discussion of Rankin, L. K.: Acute Aseptic Meningitis, Brit. M. J. **1**:54, 1932.

rare as to make one doubt that it occurs at all." It seems to us that this objection is not valid.

The possibility of a relationship to syphillis has received the support of some authors. However, in the face of persistently negative serologic tests, it would seem that such a relationship is untenable.

From a review of the reported cases it appears probable that we are dealing with a filtrable virus. Whether or not the same virus has always been responsible for all of the reported cases of this type remains a question. If the same virus is responsible, one must give consideration to the thought expressed by Eckstein that the symptomatology depends on what part of the nervous system has been affected by the virus; viz., if the virus affects the cord, one speaks of the poliomyelitic form of epidemic encephalitis. Berkesy [33] gave credence to this idea also. Eckstein, moreover, stressed the fact that according to the epidemiologic condition in each special case, this type of illness is an abortive form of either poliomyelitis or epidemic encephalitis. Blanco and Bertrand,[34] however, believed that the results of examination of the spinal fluid are merely a reaction of the reticulo-endothelial system, regardless of the producing agent.

The fact that in no one instance has paralysis resulted in the several hundred reported cases of this symptom-complex would seem to speak against a poliomyelitic virus of the usual strain. On the other hand, the development of a parkinsonian syndrome and the presence of herpes in some cases lend support to the probability of an encephalitic origin. The large number of lymphocytes in the spinal fluid, however, is not in accordance with what is ordinarily found in epidemic encephalitis. The presence of a high sugar content in the spinal fluid in our series also favors the theory of an encephalitic origin. The spinal fluid sugar was definitely above 75 mg. per hundred cubic centimeters in all of our cases in which it was recorded. In case 2 there was a change in the type of cell in the spinal fluid during the course of the illness, but unlike the findings in poliomyelitis there was a preponderance of lymphocytes at the outset. In our series, as well as in most of the reported cases, there were no prodromal symptoms of irritability and gastro-intestinal disturbances, which are so often associated with poliomyelitis, but rather an infection of the upper respiratory tract, which so frequently accompanies epidemic encephalitis.

Three of our cases occurred during the winter months and four during the spring and summer. Case 8 alone occurred during an

33. Berkesy, M.: Ueber Fälle von epidemisch auftretender Meningitis serosa im Sommer 1931 in Szeged, Wien. klin. Wchnschr. **45**:879, 1932.

34. Blanco, L. V., and Bertrand, J. C.: Estado meningeo simulando la meningitis tuberculosa, Arch. am. de med. **7**:122, 1931.

epidemic. In the summer of 1931 there was an unusually large number of cases of poliomyelitis in Brooklyn, but we were unable to demonstrate an epidemiologic relationship in our case.

CONCLUSIONS

1. The cases in our series conform to those reported by various authors under different names, all of them presenting the characteristic features of a mild meningitis and a marked lymphocytic pleocytosis in a clear spinal fluid.

2. The course of the illness is relatively short, and the prognosis is good.

3. It seems probable that the cause is a filtrable virus which is capable of calling forth a marked lymphocytic reaction in the spinal fluid.

4. Evidence is accumulating to show that it is not a disease *sui generis* but is related either to poliomyelitis or to epidemic encephalitis, most probably to the latter.

5. If this is so, then this is a form of epidemic encephalitis which has heretofore not been recognized as such, and which, because of its good prognosis, should receive attention.

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SYMPTOMATIC INFLAMMATION

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Inflammation is generally understood to be a series of phenomena involving the vessels and tissues of the living organism. It is a reaction to the influence of some injurious agent that may be physical, chemical, toxic or infectious. Apparently, inflammation takes place to protect the organism by removing the injurious agent and checking its further spread. In addition, inflammation may prepare for the healing process. It is also known that the destruction of tissue in itself may produce some kind of an injurious agent capable of exciting inflammation. General pathologists, such as Aschoff [1] and others, call this type of reaction, which is associated with tissue destruction and repair, secondary or reparative inflammation to distinguish it from the primary or defensive inflammation. This secondary or reparative type of inflammation was observed in the central nervous system in the course of neuropathologic studies by Spielmeyer,[2] who called it symptomatic inflammation. Neubürger [3] showed that in a few cases of encephalomalacia one sees vascular infiltration by gitter cells and lymphocytes at the periphery of the lesion and sometimes a thick lymphocytic coating about the big vessels, especially the veins. Schob,[4] in his textbook, stated that many authors have noted lymphocytic vascular infiltration in familial amaurotic idiocy. Wohlwill [5] reported a case of acute and rapidly progressing funicular spinal cord disease (subacute combined sclerosis) with the pathologic condition of perivascular lymphocytic infiltration, limited to the diseased area and parallel in intensity to the amount of degeneration present. He also reviewed the literature on this subject and concluded that there is

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From the Deutsche Forchungsanstalt für Psychiatrie, Kaiser Wilhelm Institut.

1. Aschoff, L.: Pathologische Anatomie, Jena, 1928, vol. 1, p. 581.

2. Spielmeyer, W.: (*a*) Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 425; (*b*) Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930; (*c*) Vergleichend anatomische Betrachtungen über einige Encephalitiden, insbesondere über den Typus der Impfencephalitis, Ztschr. f. Hyg. u. Infektionskr. **113**:170, 1931.

3. Neubürger, K., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7, p. 570.

4. Schob, F., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, vol. 11, pt. 7, p. 952.

5. Wohlwill, F.: Funikuläre Myelose und funikuläre Myelitis, Deutsche Ztschr. f. Nervenh. **117**:776, 1931.

one type of so-called funicular spinal cord disease associated with inflammation, which he called funicular myelitis, and a second type, not associated with inflammation, called funicular myelosis. Bodechtel,[6] writing on the histopathology of funicular spinal cord disease, mentioned the frequent presence of perivascular lymphocytic infiltration and maintained that any form of severe destruction of tissue in the central nervous system is practically always associated with an exudation of leukocytes, lymphocytes and plasma cells. Greenfield[7] wrote: "It is probably true that the breaking down of nervous tissue, however produced, calls forth a reaction by the cells lining the Virchow-Robin space." He explained this reaction as due to products of disintegration of nerve tissue, especially myelin. Therefore, although "symptomatic inflammation" has been noted by various authors, no systematic study of the subject has been made as yet, and one is unable to say whether there is any difference between symptomatic inflammation and primary defensive inflammation.

Having access to rich material in the Deutsche Forchungsanstalt für Psychiatrie, Kaiser Wilhelm Institut, I have attempted to study the phenomenon of inflammation in conditions which are not generally considered inflammatory.

ARTERIOSCLEROTIC ENCEPHALOMALACIA

Cases of arteriosclerosis of the cerebral vessels, with softening, were chosen first for study, since in such conditions one can be certain of the noninflammatory nature of the lesion. Sixty-five brains served as material for this investigation. These showed lesions, often multiple, at different stages of destruction and in various regions of the brain.

Neubürger, writing on arteriosclerosis,[3] showed clearly that in the early stage of softening—*Erbleichung*, as it is called by Spielmeyer—clumps of perivascular polymorphonuclear leukocytes appear around the vessels in the infarcted tissue. When Nissl produced areas of softening experimentally some fifty years ago, he described in them the presence of polymorphonuclear leukocytes, which rapidly disappeared as the lesion developed. Recently, Cone and Barrera[8] reported the presence of large focal collections of polymorphonuclear leukocytes in the brains of three patients who died five days after cerebral insults. Also, they succeeded in producing a similar reaction experimentally in dogs by artificially introducing various kinds of emboli into the carotid arteries.

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6. Bodechtel, G.: Zur Histologie der funikulären Spinalerkrankung mit besonderer Berücksichtigung bei der perniciösen Anämie zu sehenden Grosshirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**:104, 1931.

7. Greenfield, G., in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, p. 221.

8. Cone, W., and Barrera, S. E.: The Brain and the Cerebrospinal Fluid in Acute Aseptic Cerebral Embolism, Arch. Neurol. & Psychiat. **25**:523 (March) 1931.

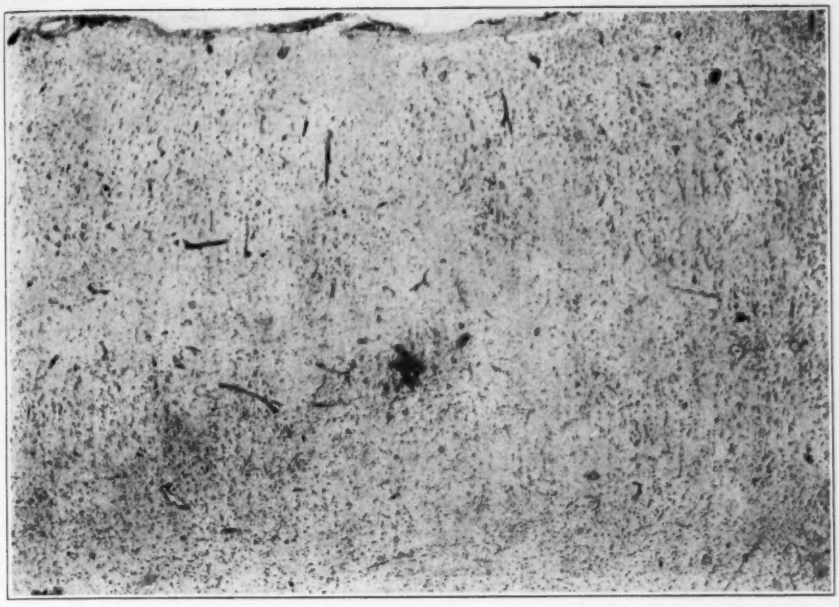

Fig. 1.—Section of a cortex from a patient with air embolism, showing a focal collection of leukocytes in a freshly softened area in the deeper layers of the cortex.

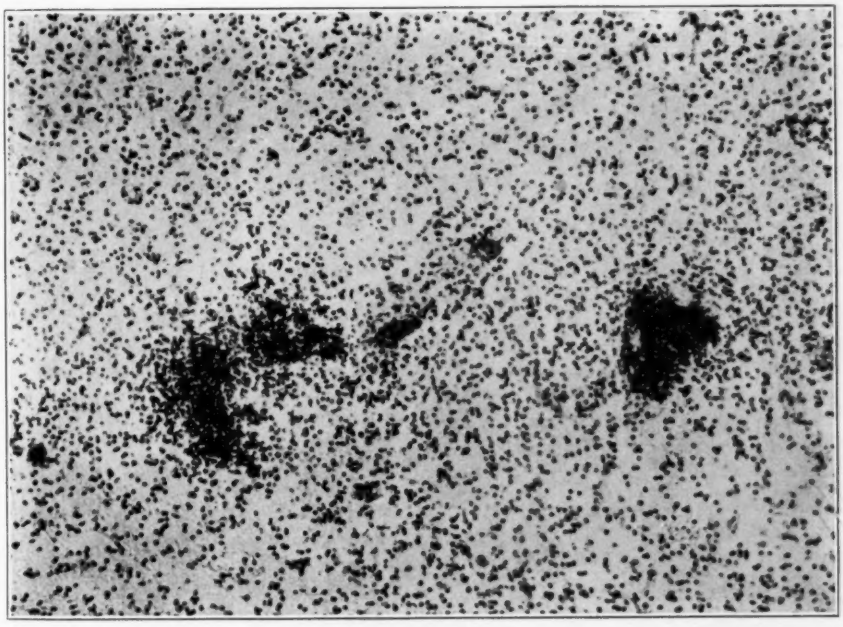

Fig. 2.—Section of cortex from a patient with early arteriosclerotic softening, showing several clumps of leukocytes.

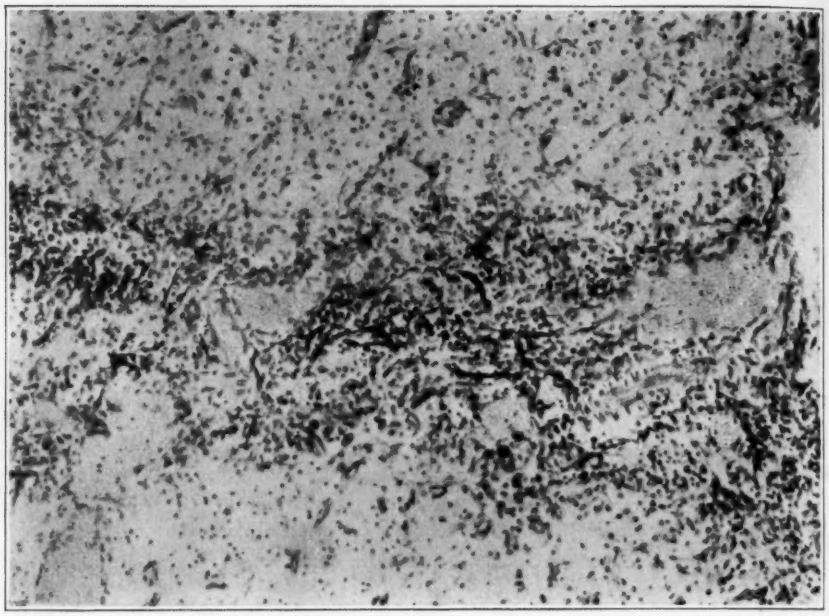

Fig. 3.—Section from another patient with arteriosclerotic softening in the cortex, showing beginning mesenchymal proliferation and gitter cell formation in the first cortical layers. Meningeal infiltration by macrophages, lymphocytes and plasma cells is also present. The elongated darkly stained cells are chromatophores.

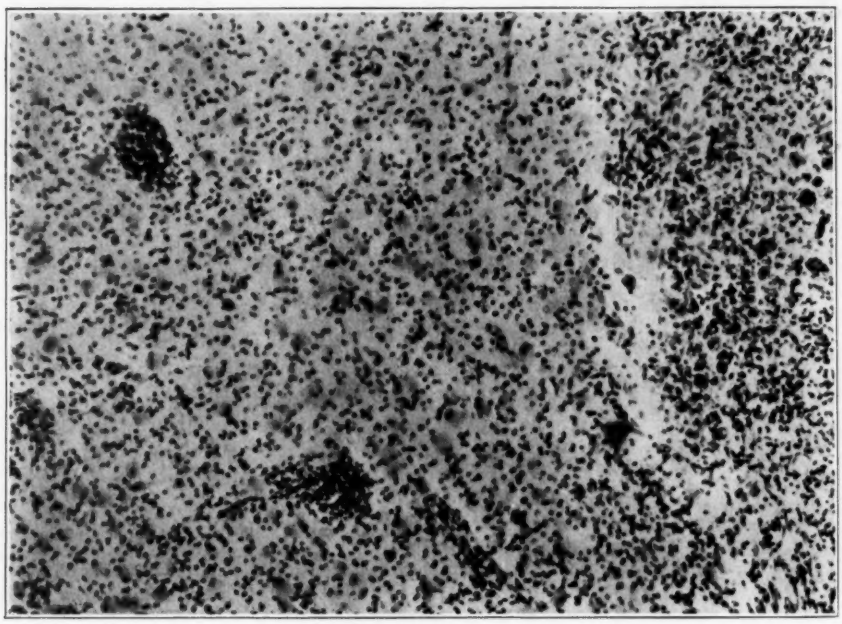

Fig. 4.—Section from a patient with arteriosclerotic softening, showing perivascular infiltration in the region of the *gemästete* glia cells near the softening (right).

In the present study, six cases of early softening, in which the cerebral insults occurred from four to six days before death, showed similar pictures. In the infarcted area the ganglion cells appeared to fade away (in Nissl-stained preparations) and the glia cells showed regressive changes. Polymorphonuclear leukocytes engorged the vessels, infiltrated the perivascular spaces and wandered into the surrounding tissue, forming leukocytic clumps (figs. 1 and 2). These clumps resembled miliary abscesses, except that they occurred only in the infarcted area and not in other sections of the brain, which makes it certain that they represent special reaction to acute necrosis shown experimentally by Nissl and Cone and Barrera. There was also, at times, a leaking out of red blood corpuscles. In cortical softening these collections of polymorphonuclear leukocytes usually occur in the deeper layers of the cortex. One sees the first sign of tissue destruction in such leukocytic clumps and in the granules of fat, which are lying free in the tissue or are taken up by the leukocytes. It is almost certain that this outpouring of leukocytes is due not to hemostasis or to injury of the wall of the vessel, but to a definite chemotactic influence exerted by tissue undergoing acute necrosis.

In the meninges overlying the infarcted area, one sees distinctly, at a little later stage, proliferation of the connective tissue and infiltration by macrophages, leukocytes, lymphocytes and plasma cells, which may suggest the picture of an infectious process (fig. 3). Most of the macrophages appear young and contain no foreign bodies, and, in regions where there are small pial hemorrhages—a not unusual observation—or where the underlying cortex shows softening, with gitter cells, these macrophages appear to take up fat in fine granules. The fat from the necrotic tissue seems to be transported to the meninges either through the perivascular spaces or by direct invasion of the subarachnoid space, when the softening is close to the surface. As the process becomes older, the leukocytes degenerate and disappear, while the lymphocytes and macrophages may remain, the latter taking up more and more fat. Thus, in the later stages, one observes that practically all the macrophages are loaded with fat. Meningeal proliferation and infiltration occur near these lesions before the appearance of any reactive phenomena in the brain substance itself. This meningeal reaction has the same appearance (and probably also the same function) as the reaction which takes place in the brain substance, only it develops earlier and the meninges evidently suffer less from the circulatory disturbance.

Soon afterward, mesenchymal proliferation occurs in the parenchyma of the brain in the periphery of the lesion. With this endothelial proliferation one sees definitely gitter cells formed from the endothelium. It is probable that in total necrosis most of the gitter cells have a mesenchymal origin. As the mesenchymal tissue and the glial elements start to proliferate, with resultant formation of gitter cells, one sees practically always a reaction of the mononuclear cells, particularly the plasma cells. Often many plasma cells and some lymphocytes may be seen lying freely between the meshwork of newly formed gitter cells and the actively proliferating endothelial cells or in the perivascular spaces. Sometimes a large number of mast cells is seen. In total necrosis this infiltration usually occurs in the peripheral portions of the lesions, where the scavenging and regenerating processes begin. In partial necrosis the glia cells play a large part in the formation of gitter cells. Further, it is observed that in regions where there is marked mesenchymal proliferation the infiltration consists more of plasma cells than of lymphocytes, and that in regions where there is less active mesenchymal proliferation the infiltrating cells are mostly lymphocytes. This is not unlike the picture in the capsule of an abscess, when infiltration of plasma cells is seen, associated

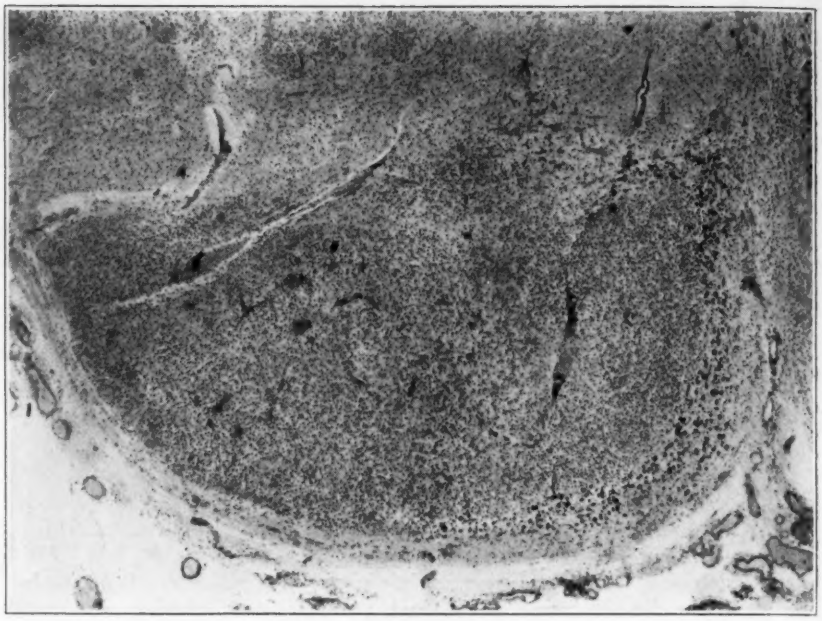

Fig. 5.—Section of medulla oblongata, with secondary degeneration of one of the pyramidal tracts, showing perivascular infiltration.

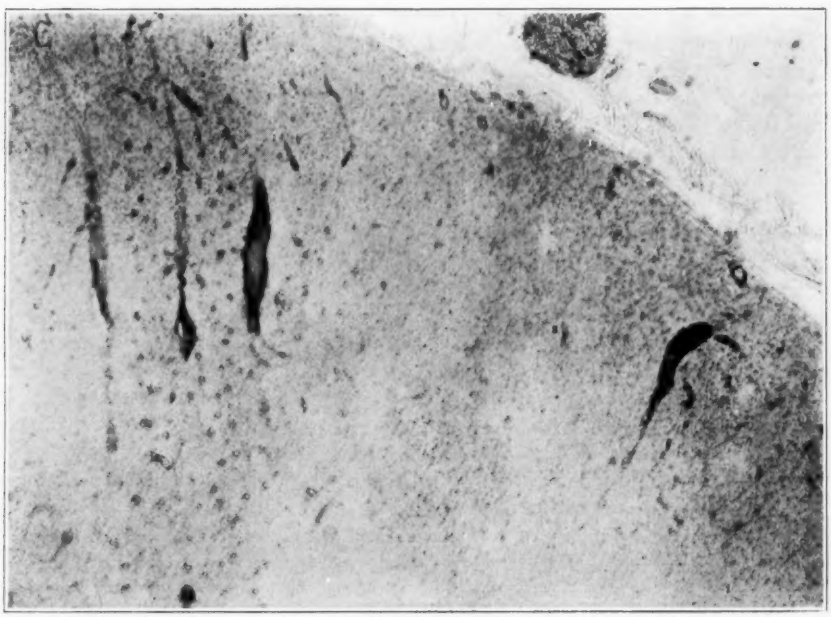

Fig. 6.—Section from a patient with funicular spinal cord disease, showing perivascular infiltration in the posterior medial fissure and in the posterior and lateral columns bordering the diseased areas.

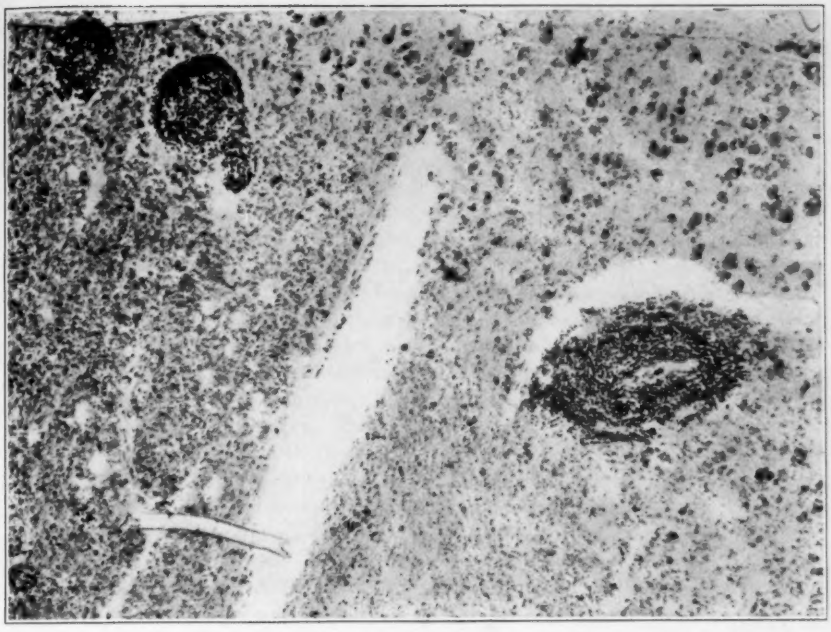

Fig. 7.—Scarlet red-stained preparation from a patient with funicular spinal cord disease, showing thick perivascular lymphocytic infiltration at the edge of the lesion, where many fat-loaded gitter cells are lying free in the tissue.

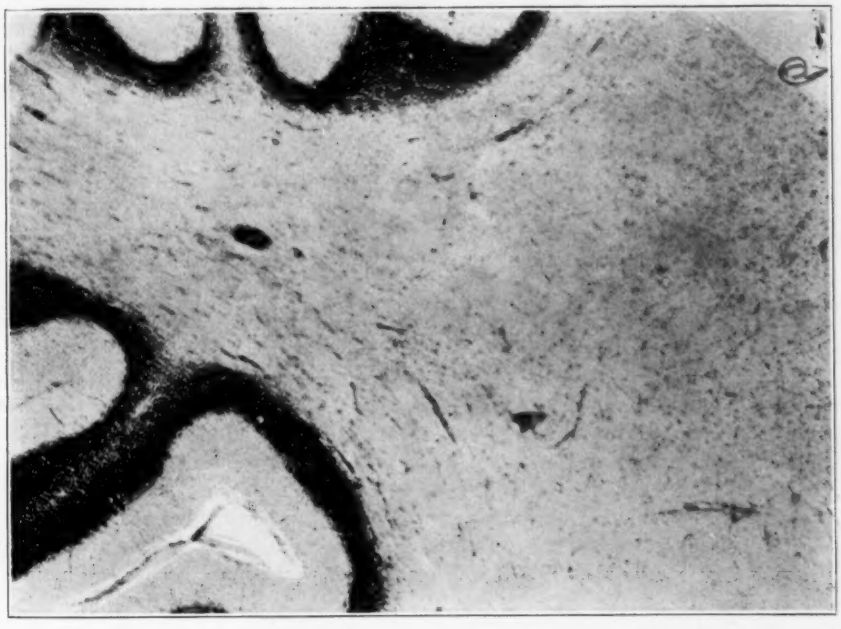

Fig. 8.—Section of cerebellum from a patient with familial amaurotic idiocy, with rapid and severe destruction of myelin, showing perivascular infiltration at the border of the demyelinated area.

with marked proliferation of mesenchymal tissue. This suggests that probably the same irritant which excites the proliferation of the connective tissue may be responsible for the calling out of the plasma cells in particular.

Most of the material examined, from patients who had died some days after the cerebral insult, showed a well established softening, with the presence of gitter cells and *gemästete* glia cells. In practically every case thus far studied some mononuclear perivascular infiltration was present. This reaction was absent only in cases in which the lesion was small and limited to the cortex or in which the lesion was old and organized, with the formation of glial scars. These negative observations can be explained by the supposition that in small lesions the injurious agent produced through tissue destruction was probably insignificant in quantity, and that in old lesions it had probably been neutralized or removed. When mononuclear perivascular infiltration was present, it was always found at the edge of the lesion lying in the mass of *gemästete* glia cells next to the actively phagocytic gitter cells (fig. 4). The infiltrating cells, chiefly lymphocytes, collected about arteries and veins in almost equal numbers, though there was perhaps a slight predominance of periarticular infiltration in early lesions and of perivenous infiltration in later ones. No one has observed infiltration around small vessels and capillaries, such as occurs in dementia paralytica and other infectious conditions, nor has perivascular glial proliferation, such as occurs in postvaccinal encephalitis, been reported. This infiltrative reaction occurred most actively in the white matter and not around vessels in the cortex near the lesion, where the ganglion cells were not totally destroyed. At the height of its activity there was marked proliferation of gitter cells and *gemästete* glia cells. As the process became older and the perivascular spaces were filled with the fat-loaded gitter cells, the infiltrative process subsided and a picture that may be called pseudoinfiltration, showing chiefly gitter cells with a few lymphocytes, presented itself.

(*a*) *Secondary Degeneration of the Pyramidal Tracts.*—In our study of arteriosclerotic encephalomalacia, fifteen brains were examined in which degeneration of one or both pyramidal tracts had occurred as the result of a primary lesion in the region of the basal ganglia or in the pons. Most of the sections were taken through the medulla oblongata at the level of the inferior olivary nuclei. Except in one case, in which there was replacement by abundant glia nuclei and a few gitter cells that contained fat, the degenerated pyramidal tracts showed a slight lymphocytic perivascular infiltration (fig. 5). The infiltration occurred around the arteries as well as the veins and in and around the degenerated tract itself. It was rarely intense, but was always distinct and was most pronounced when there was active removal of fat by the gitter cells, which lay freely scattered in the tissue. As the process grew older and the gitter cells gathered in the perivascular spaces, the inflammatory phenomena gradually subsided.

(*b*) *Arteriosclerotic Vessels.*—Lymphocytic infiltration around hyalinized arteriosclerotic vessels has been repeatedly observed. Of the thirty-five brains with arteriosclerotic encephalomalacia which were studied, twenty-nine were observed to have definite infiltrations, in most cases in the perivascular Virchow-Robin spaces, but also involving the intimal coats themselves, in which marked intimal proliferation or hyalinization was present. The infiltration was present in vessels showing marked arteriosclerosis and thickening of the intima, which might be hyalinized or pseudocalcified and which might show progressive changes in the lining cells. In many cases infiltrations were present about vessels in one region and not about those in another, although the vessels in both regions seemed to be

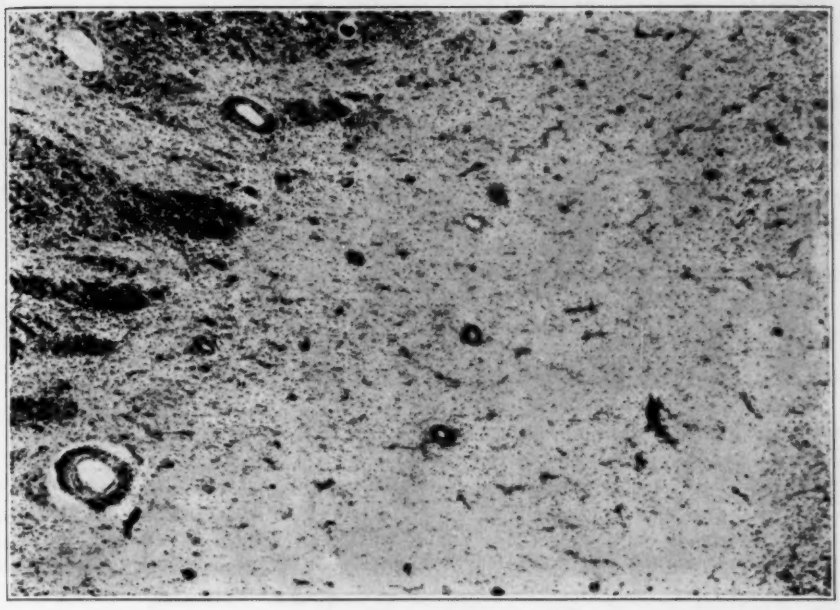

Fig. 9.—Myelin-stained preparation from a patient with familial diffuse sclerosis, showing perivascular infiltration in, and bordering on, the area of demyelinization, where there is also marked glial proliferation.

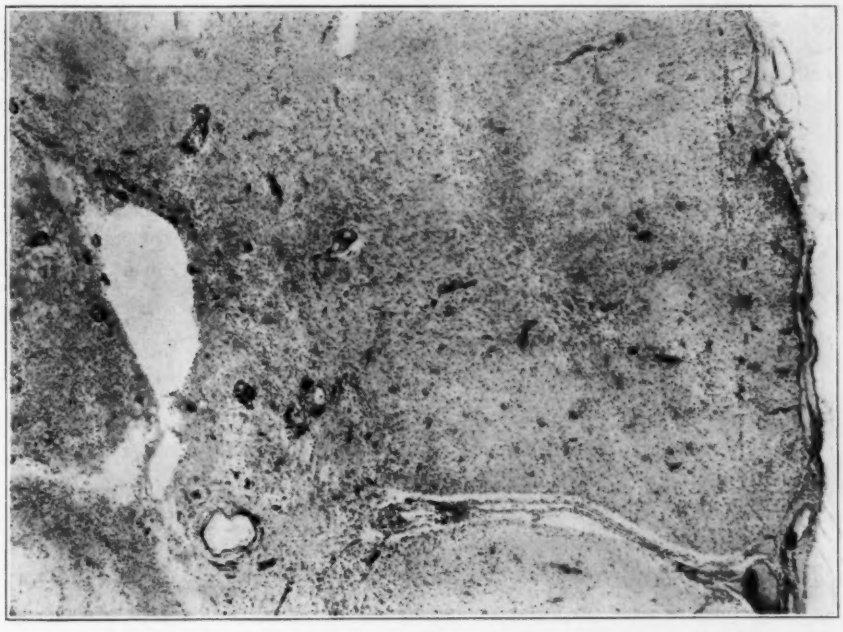

Fig. 10.—Section from a patient with compression of the spinal cord, showing marked perivascular infiltration at the edge of a region of considerable softening. There is definite mesenchymal proliferation here, and the infiltrative cells are mostly plasma cells.

damaged to the same extent. Hence, no definite clue was found as to the exact conditions under which this reaction occurs. In these cases the infiltration probably resulted not from the destruction of nerve tissue, but from the deposition of foreign material, such as hyalin and cholesterol, in the wall of the diseased vessel.

FUNICULAR SPINAL CORD DISEASE

In this study twenty-two spinal cords were examined, sections being taken from various segments and stained by the Nissl scarlet red and Holzer or Weigert glia fiber methods. With two exceptions, all showed distinct perivascular infiltration. Practically all the infiltrating cells were lymphocytes. In eight cases, however, a few plasma cells were also present. The mesenchymal proliferation was never prominent. The infiltration was always seen at the edge of the relatively fresh lesions and was most intense when the fat-loaded gitter cells were lying free in the tissue and not in the perivascular spaces. Within the lesion vessels were often seen with gitter cells in the perivascular spaces and with lymphocytes in the spaces leading away from the lesion. Infiltration was seen around both arteries and veins, and one had the impression that in intense infiltration the process is more periarterial (figs. 6 and 7). In appearance this reaction greatly resembles that which occurs in softening of the brain, but differs considerably from what one sees in infectious myelitis or multiple sclerosis in which inflammatory phenomena exist. This agrees with the general opinion today that funicular spinal cord disease is a degenerative, and not an infectious, disease.

OTHER CONDITIONS

The picture of perivascular infiltration by lymphocytes and plasma cells in the periphery of the lesion which is observed in arteriosclerotic encephalomalacia is seen also in other pathologic processes of the brain, e.g., hemorrhage, injuries of an apparently noninfectious nature, familial amaurotic idiocy (fig. 8) in a few instances and familial diffuse sclerosis (fig. 9). In all of these there is marked and rapid destruction of myelin in the white matter, with active removal of fat and glial proliferation. In the cases of tumor of the brain studied, perivascular infiltration was observed in a few instances in malignant metastatic tumors and rapidly growing gliomas. Perivascular infiltration seems to be always associated with destruction of tissue and removal of fat. However, the amount of material on tumors is too small to warrant any generalizing conclusions. Softening of the spinal cord from compression by tumors was accompanied also by inflammatory phenomena in the few cases observed (fig. 10).

COMMENT

From the foregoing study it is evident that, as a rule, inflammatory phenomena occur when there is a significant destruction of tissue in the central nervous system. The agent responsible for the inflammatory phenomena is probably one of the lipoid substances which constitute the main part of the products of disintegration, since lipins are normally present in great quantity in the central nervous system. It was observed that an inflammatory reaction is not so much associated with a small cortical lesion as with a small lesion of the spinal cord, which is accom-

panied by a marked reaction. This may suggest a closer relation between destruction of myelin and symptomatic inflammation.

It is generally accepted that the type of reaction is not determined by the injurious agent. In other words, similar types of reaction may occur with different kinds of injurious agents. Thus, Spielmeyer has shown that a marked glial reaction, such as is often seen in virus diseases, may also occur in ordinary bacterial (streptococcic) infection. In symptomatic inflammation, although the causative injurious agent is neither a bacterium nor a virus, the reaction is not much different from what one sees in chronic inflammatory diseases. The presence of the inflammatory reaction at the edge of the area of tissue destruction compares well with the same observation in the wall of a chronic abscess, as in both conditions the inflammatory reaction serves to localize the injurious agent and to attempt its removal.

The constant observation of the outpouring of polymorphonuclear leukocytes in the early stage of softening in the brains of man and of experimental animals makes it certain that this phenomena is not a mere coincidence or a sign of sepsis, but a part of the reaction to acute necrosis of tissue. The leukocytes, which are known to have histolytic power, are probably associated in this reaction with the dissolution of cells.

CONCLUSIONS

1. Significant destruction of tissue in the central nervous system, particularly that associated with dissolution of myelin, is accompanied by the symptomatic inflammation of Spielmeyer, as a rule.

2. The inflammatory phenomenon occurs at the periphery of the lesion.

3. The infiltrating cells are mainly plasma cells and lymphocytes. Polymorphonuclear leukocytes appear in the early stage of softening in the brain.

4. There seems to be a relationship between mesenchymal proliferation and inflammation by plasma cells.

5. The nature of this inflammatory reaction is not much different from that which occurs in a primary inflammatory reaction.

Clinical Notes

SPONGIOBLASTOMA BIPOLARE IN THE REGION OF THE HYPOTHALAMUS

Associated With Infantilism and Without Dwarfism

WALLACE B. HAMBY, M.D., CLEVELAND

Since Marie's [1] famous article on acromegaly appeared in 1886, many clinical syndromes have been ascribed to disorders of the pituitary body. Later it was shown that some of these syndromes might be produced by lesions of the hypothalamus. The exact rôles of these two structures in the production of the so-called pituitary syndromes are not yet generally agreed on. For this reason it has seemed worth while to record a case of sexual infantilism without dwarfism caused by a glioma of the hypothalamic region.

REPORT OF A CASE

History.—The patient, a man, aged 22, first came to the clinic on Jan. 28, 1931, complaining of failing vision. Examination disclosed bilateral papilledema, and he was admitted to the hospital on the same day. Six months before admission, while chopping wood, he had suddenly felt faint and dizzy. He took a drink of water, promptly vomited and experienced an excruciating headache which lasted for three days. Similar bouts of headache and emesis continued in increasing severity until six weeks before admission. Three weeks prior to admission vision had begun to fail; the left eye had become practically blind.

On admission the patient's height was 6 feet and 1 inch (185.4 cm.); he was obese, weighing 226½ pounds (102.7 Kg.). He had acquired these proportions gradually, and had always been large for his age. For the past four or five years the size of his hat had not changed, although he had required a shoe one size larger each year. Both of his grandfathers were 6 feet tall and several uncles were tall men, while his father, mother and sister were of medium height and rather obese.

His water intake had always been above normal, with definite polydipsia and polyuria for the past two years. Past illnesses included one convulsion in infancy, measles and whooping cough, and pneumonia at the age of 10.

The patient's habits were good. He enjoyed farm work, which he did very well. Although he was 22 years of age, he did not care for feminine companionship; he had never experienced an erection or a nocturnal emission. He had liked to read before the onset of visual difficulty, and there had been no impairment of memory or changes in personality.

Read at a meeting of the Chicago Neurological Society, May 18, 1933.

From the Division of Neurology and Neurosurgery, University of Chicago Clinics.

1. Marie, P.: Sur deux cas d'acromégalie, Rev. de méd. **6**:297, 1886.

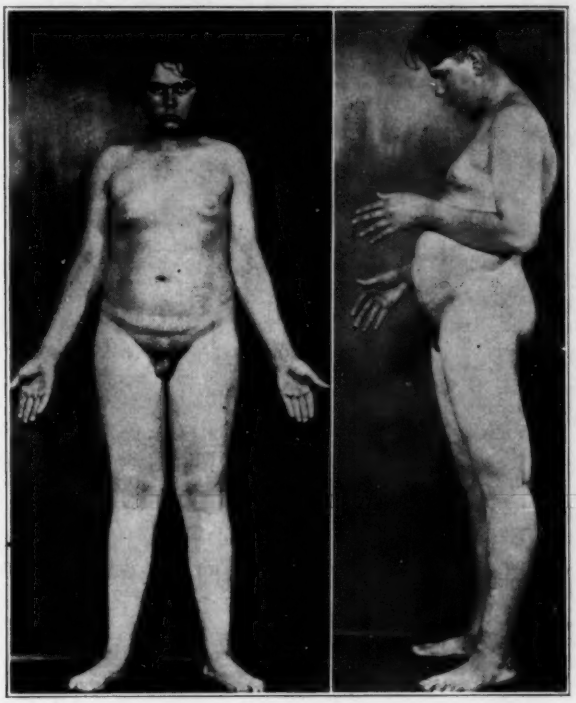

Fig. 1.—The patient, showing infantile distribution of fat and scant development of hair.

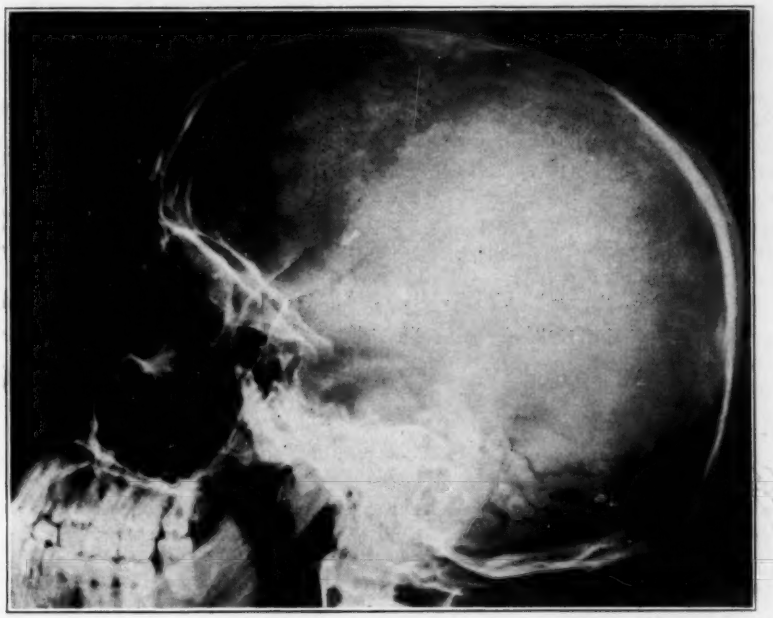

Fig. 2.—Roentgenogram of the skull, showing the suprasellar calcification and the changes in the sella turcica.

Physical Examination.—The patient was a large-framed, obese man, 185.4 cm. in height and weighing 102.7 Kg. (fig. 1). The extremities were quite large; the hands were approximately 25 per cent greater than normal size, but were symmetrical with tapering fingers; the feet required shoes of size 10. The head was of normal measure, the hat size being 7⅛. The skin was soft, like that of a baby, and the quantity of hair was diminished. He had never shaved; there was no thoracic or axillary hair, and the pubic hair was of female distribution. The penis was infantile, and the testes were very small. The voice was still high-pitched and childish. The distribution of fat was of infantile type, and the breasts were rather large. There was no prognathism; the teeth occluded normally in biting. The moderately enlarged tongue protruded in the midline without tremor.

The left eye diverged from 10 to 15 degrees, and this was increased on attempts to converge. The right pupil measured 6 mm. and reacted to light, while the left measured 3.5 mm. and reacted slowly. Homatropine hydrobromide had been instilled five days prior to this examination and may have influenced the pupils even at this time. The disks showed edema of 2.5 diopters on the left and 3 diopters on the right, with tortuous veins and several small retinal hemorrhages. Examination of the visual fields showed a binasal hemianopia, the field on the left being reduced to a temporal island. Hearing was normal, and in general, apart from the eyes, neurologic examination gave normal results.

Clinical Impression.—The clinical impression was gigantism associated with adiposity and genital dystrophy, due to a primary adenoma of the hypophysis with pressure on the hypothalamus.

Roentgenograms.—Roentgenographic examination of the skull (fig. 2) revealed a diffusely calcified mass, about 3 cm. in diameter, 1.5 cm. above the posterior clinoid process of the sella, extending both to the right and to the left of the midline. The posterior clinoid processes were practically decalcified, while the anterior clinoid processes were intact. The floor of the sella turcica appeared to be depressed into the sphenoid sinus. There was no evidence of acromegaly, nor was there any other abnormality in the skull.

Roentgen examination of the extremities revealed unfused epiphyses of the lower ends of the radii and ulnae and of the carpal, metacarpal and phalangeal bones of both hands. There was no terminal tufting of the distal phalanges, as is commonly seen in acromegaly. There was considerable elongation of the metacarpal and phalangeal bones. There was fragmentation of the terminal epiphysis (Koehler's disease) of the second metatarsal bone. The other epiphyses of the feet were fused. The diagnosis of the roentgenologist was: calcification of a suprasellar tumor, probably of Rathke's pouch.

Laboratory Studies.—A dextrose tolerance test revealed a mildly increased tolerance. The basal metabolic rate was —11 per cent. Examination of the blood and urine revealed nothing abnormal, and the Wassermann and Kahn reactions were negative.

Diagnosis.—A diagnosis was made of calcified suprasellar tumor.

Operation.—On Feb. 3, 1933, under ether anesthesia, a right transfrontal approach to the suprasellar region was made (Dr. Bailey). The brain was found to be under increased tension. This was relieved by puncturing the right lateral ventricle, revealing marked hydrocephalus. The right optic nerve, the chiasm and the left optic nerve were exposed. The chiasm was flattened and displaced forward by a tumor mass which could be seen bulging between the optic tracts. No tumor could be seen under the optic nerves. The internal carotid artery could be seen pulsating in the angle between the right optic nerve and tract. Attempted aspira-

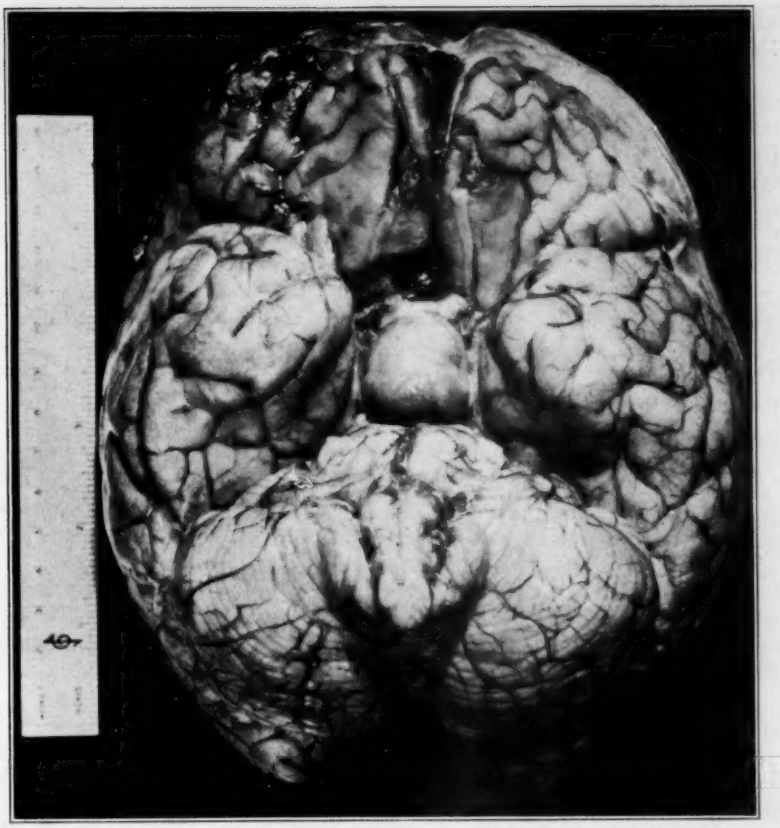

Fig. 3.—Base of the brain, showing tumor of the hypothalamus and pressure cone.

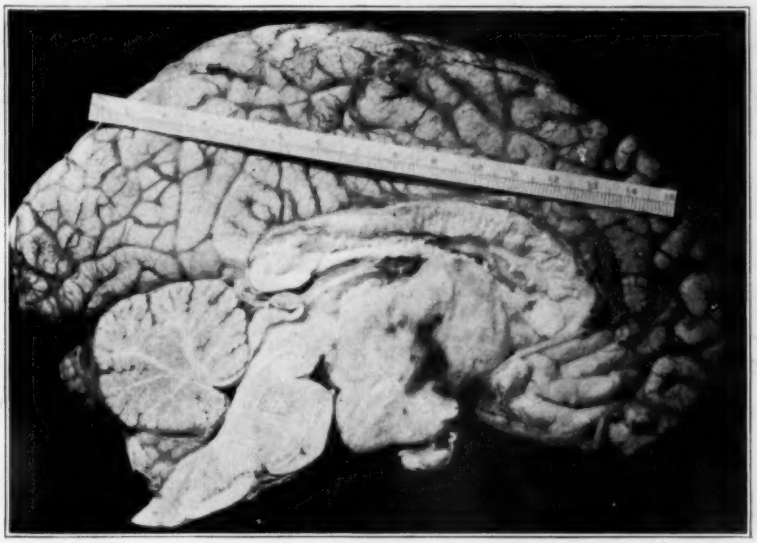

Fig. 4.—Sagittal section of the brain.

tion of the tumor mass yielded no cystic fluid. The anterior cerebral artery was retracted from the right optic nerve and an attempt was made to free the tumor, but it was not possible. A small fragment of tumor was removed for microscopic examination, and brisk bleeding resulted. After hemostasis was obtained the dura was closed; the bone flap was replaced and the incision closed.

Postoperative Course.—The patient never regained consciousness. The temperature and blood pressure began to rise. Ventricular punctures and measures employed to control the hyperpyrexia were without benefit. On the next day the temperature was 106 F. and the blood pressure was 170 systolic and 80 diastolic. The patient died at noon, about twenty-four hours after the operation.

Necropsy.—This was performed two hours after death. The general observations were: hypoplasia of the reproductive organs; fatty metamorphosis of the liver; slight hypertrophy of the myocardium; subpleural calcified tuberculosis; an accessory spleen; Koehler's disease of the second right metatarsal bone.

Examination of the brain revealed marked hydrocephalus. In the base of the brain (fig. 3) just above the hypophysis was a tumor mass which measured 3 cm. in anteroposterior diameter and 2.5 cm. in lateral diameter. It extended from the optic chiasm, which was partially surrounded by but seemed not to be involved in the tumor, backward to the anterior surface of the pons, which was flattened. The hypophysis was attached by an apparently normal stalk to the under surface of the tumor, 0.5 cm. behind the optic chiasm. The hypophysis was somewhat flattened, but not otherwise involved in the growth.

Median sagittal section (fig. 4) revealed the tumor mass filling practically the entire third ventricle; it was roughly spherical and 5 cm. in diameter. Its cut surface was reddish gray, with some whitish and hemorrhagic areas in the center. The foramina of Monro were pushed far posteriorly by the tumor and there was marked hydrocephalus of the lateral ventricles. The anterior commissure and mamillary bodies were not distinguishable.

Microscopic examination of the tumor (fig. 5) showed it to be a fairly cellular lesion composed of fusiform cells with a parallel arrangement in bundles which interlaced and ran in all directions. The typical tumor areas were only moderately vascular, but there were areas of hemorrhagic infiltration and degeneration in which the vascularity was increased. Calcium salts were found in the walls of some of the vessels.

Typical cells (fig. 6*A*) were of long spindle shape with an abundance of cytoplasm. The cells did not attach themselves to the blood vessels by "sucker-feet" as is common in the astroblastic series, and astrocytes were not found in the tumor. The nuclei were fairly large, ovoid in longitudinal section and round in transverse section, with well defined nuclear membranes. The finely granular chromatin was evenly distributed, and a distinct nucleolus was present in most of the nuclei; multinucleated cells were common, but no mitoses were seen. The rather voluminous cytoplasm (fig. 6*B*) streamed away from the nucleus in two long processes which frequently split near the ends. In some cells the cytoplasm was hypertrophied enormously and pushed the nucleus to the periphery.

Reticulin was confined to the walls of the blood vessels and was not found between the cells in the tumor. In areas of degeneration there was an increase in reticulin coincident with the increased vascularity.

Pathologic Diagnosis.—The diagnosis was spongioblastoma bipolare.

Sections of the hypophysis stained with hematoxylin and eosin, Bailey's neutral ethyl violet-orange G and acid violet-eosin revealed no abnormality. The percentage of eosinophils and basophils seemed normal.

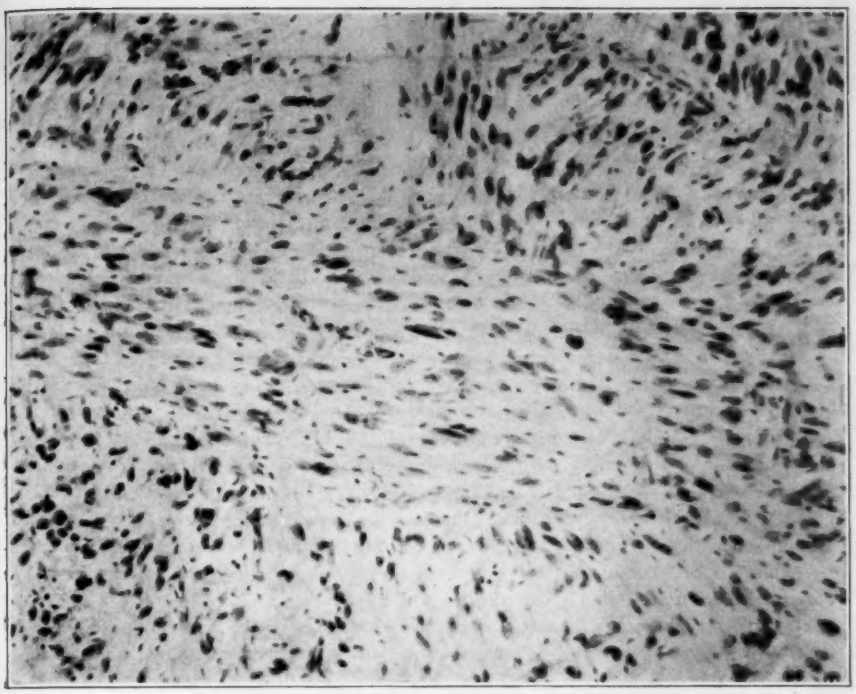

Fig. 5.—Section showing interlacing bundles of fibers. Hematoxylin and eosin; × 150.

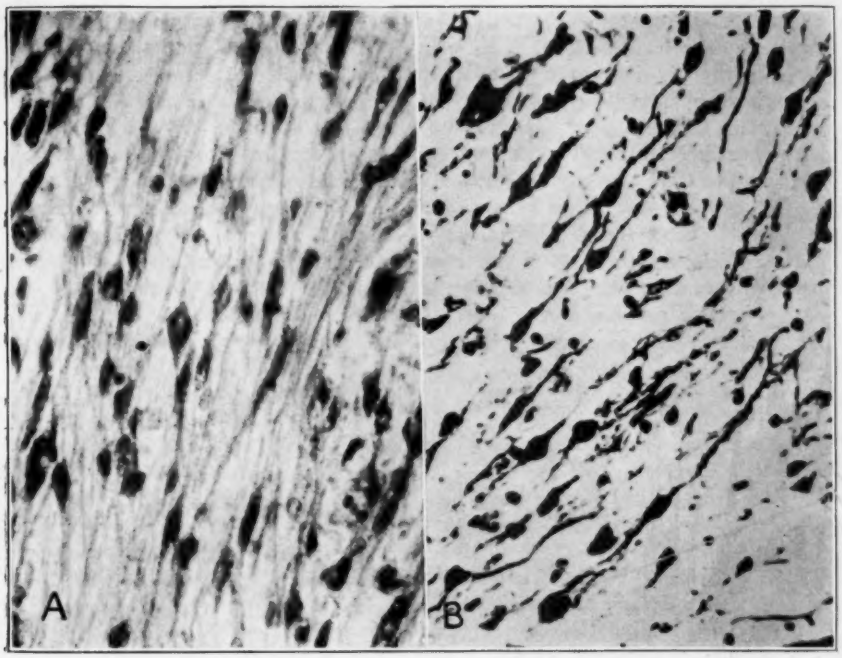

Fig. 6.—*A*, spongioblasts. Hortega's silver carbonate method; × 300. *B*, spongioblasts. Wilder's method; × 300.

COMMENT

It has been established that the degree of activity of the hypophysis is responsible for normal development, overdevelopment or underdevelopment of the skeletal system. Hypopituitarism produces pituitary dwarfs by arresting growth in childhood, and sexual dystrophy in adults whose growth already has been completed. Hyperpituitarism, on the other hand, produces gigantism in young subjects whose skeletons are still capable of growth, and acromegaly in those whose epiphyses have closed. As Launois and Roy [2] stated in 1904, "Gigantism is the acromegaly of subjects whose epiphyseal cartilages have not ossified, whatever be their age." It has been found that all persons with acromegaly have fused epiphyses and that all patients with arrested growth, whatever their size and age, have ununited epiphyses.[3]

While the pituitary adenoma alone is responsible for acromegaly, it became recognized early that many other tumors may produce hypopituitarism. The most common of extrasellar lesions affecting the pituitary body are gliomas of the optic chiasm, tumors of the hypothalamus, tumors and cysts arising from remnants of Rathke's pouch and even a hydrocephalic third ventricle. Their influence can best be explained by pressure on the gland, or possibly by disturbances of the neural connections [4] between the hypothalamus and hypophysis.

Infantilism, however, includes other factors than growth. The adiposogenital dystrophy that is a part of this state may be purely hypothalamic in origin,[4] while destruction of the hypophysis itself can also produce genital dystrophy. Cushing,[3] considering the multiple factors present in infantilism, concluded that "it is unwise to lay too great stress on anything other than the possibility of an indirect hypophyseal participation in the dwarfed stature characterizing the many types of infantilism."

In the case reported here, if one supposes the sexual infantilism to be due to diminution of the secretory activity of the hypophysis, it is surprising that there was no undergrowth. Although one may be hesitant to speak of gigantism in this case, because the boy came of a family of tall people, the seeming paradox of gigantism and infantilism has been repeatedly described in other cases. The case of Cushing's famous giant Turner, who was 8 feet 4 inches (254 cm.) tall, was such an example of arrested skeletal development and infantilism. His epiphyses were incompletely ossified. The lesion was a gland-destroying pituitary cyst.

One need not discuss the symptomatology of tumors in the region of the third ventricle. That there is no syndrome of the third ventricle per se was pointed out by Weisenburg [5] in 1910. At least three different trains of symptoms are possible, depending on which part of the ventricular wall is involved.[4]

The most common site for the occurrence of spongioblastomas is in this neighborhood, as Bailey and Cushing [6] pointed out in their original monograph on the

2. Launois, P. E., and Roy, P.: Etude biologique sur les géants, Paris, Masson & Cie, 1904.

3. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

4. Fulton, J., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1 (Jan.) 1929.

5. Weisenburg, T. H.: Tumors of the Third Ventricle, with the Establishment of a Symptom Complex, Brain **33**:236, 1910.

6. Bailey, P., and Cushing, H.: Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1916.

classification of gliomas. This tumor demonstrates the histologic characteristics of this type of glioma in a fairly typical manner. Spongioblastomas rarely contain enough calcium to be visible,[7] and surprisingly little calcium was found in this tumor at autopsy in view of the fact that sufficient calcification was seen in the roentgenograms to make the diagnosis of a calcified tumor of Rathke's pouch seem most probable.

DISCUSSION

DR. VICTOR E. GONDA: I understand that the patient had binasal hemianopia. How do you explain that in the case of a single tumor?

DR. R. P. MACKEY: Was there any evidence of primary or secondary optic atrophy?

DR. W. B. HAMBY: No evidence of primary optic atrophy was noted. There was edema of 2 or 3 diopters, but no atrophy.

DR. PERCIVAL BAILEY: There was no real binasal hemianopia but a defect in the visual fields. I have never seen a cleancut binasal hemianopia.

DR. A. B. YUDELSON: Was there a diminution of visual acuity in these fields?

DR. W. B. HAMBY: Yes, the patient was practically blind in the right eye. I do not recall the exact measurements.

DR. PERCIVAL BAILEY: In this case there was no evidence of backing up of a possible secretion. Although, so far as we could determine, the third ventricle was completely occluded in the lower portion, there was no alteration of the posterior lobe of the hypophysis. It appeared normal in structure.

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7. Bailey, P., and Eisenhardt, L.: Spongioblastomas of the Brain, J. Comp. Neurol. **56**:391, 1932.

FAMILIAL SPASTIC PARALYSIS

ARTHUR H. JACKSON, M.D., WASHINGTON, CONN.

Familial spastic paralysis is in many ways one of the most interesting of the heredofamilial diseases of the central nervous system. It may occur in a simple form as a pure spastic paraplegia, as it was first described by Strümpell,[1] in 1886, but is apt to present itself in a complex form and may, in fact, be one of the most bizarre of all its group. It may occur in only two of a large number of siblings or in all of the members of a single generation. A single generation may be affected, or the disease may crop out in as many as six generations. While many cases have been reported in the European medical literature, and particularly in the literature of the northern countries, few detailed family histories have been published in American medical journals. In fact, with the exception of the excellent articles by Rhein,[2] Williams[3] and Paskind and Stone,[4] practically no comprehensive reports have been published in this country since the first of the century. It seems, therefore, that a detailed report of another family afflicted with this comparatively rare disease should be of interest.

REPORT OF CASES

Family History.—The S. family lived in a small industrial town in the Naugatuck Valley, in the western section of Connecticut. The parents were natives of Poland; the oldest child was also born there. The other six children were born in two different towns in New York and Massachusetts. The father was a healthy and physically strong mill operator, who had always enjoyed excellent health. The mother was obese, and in the fifties. She had always been well until the last few years before examination, during which she had been more or less chronically ill with cardiovascular-renal disease. The father's parents showed no evidence of disease of the central nervous system, and his only brother and all of his nine nieces and nephews were healthy. The mother's father was free from any suggestion of the disease, but her mother had been paralyzed most of her life. An exact clinical history of this woman could not be obtained, but Mrs. S. stated that the paralysis was confined to one arm and one leg, and that its onset was acute after a bad fall during childhood. There was little to suggest that her mother was afflicted with the disease under discussion. The brother and sister of Mrs. S. and their seven children were well. The parents were not related, and they and their children had negative Wassermann reactions of the blood.

From the Department of Internal Medicine, Yale University School of Medicine, and the Neurological Service of the Waterbury (Conn.) Hospital.

1. Strümpell, A.: Arch. f. Psychiat. **17**:217, 1886.
2. Rhein, J. H. W.: J. Nerv. & Ment. Dis. **44**:115, 1916.
3. Williams, G. H.: J. Nerv. & Ment. Dis. **47**:427, 1918.
4. Paskind, H. A., and Stone, T. T.: Familial Spastic Paralysis: Report of Three Cases in One Family and Observation at Necropsy, Arch. Neurol. & Psychiat. **30**:481 (Sept.) 1933.

SIBLING 1.—Frank S., aged 29, who was born in Poland, began to have difficulty in walking when he was 14. This was particularly noticeable when he walked down-hill or down-stairs, and there was a tendency to pitch forward. This condition had progressed slowly during the last fifteen years; he grew tired easily and occasionally lost his balance, always pitching forward on his face. He wore out the toes of his shoes about equally. He had no other difficulty and was able to do bench work in a factory. He had never had an acute illness. The cranial nerves were entirely normal. The positive neurologic findings were: (1) moderate hypertonia of both arms; (2) marked spasticity of all of the muscles of the legs, with some weakness of the abductor groups and contraction of the gastrocnemius and soleus; (3) a positive Babinski sign on both sides; (4) bilateral ankle clonus; (5) a positive Kernig sign on both sides; (6) marked ataxia in performing the heel-knee-shin test; (7) hyperactive deep reflexes throughout, but with those of the legs greater than those of the arms; (8) a spastic gait, with a tendency to drag both feet; (9) inability to stand straight, the knees and hips being slightly flexed. There were no sensory disturbances.

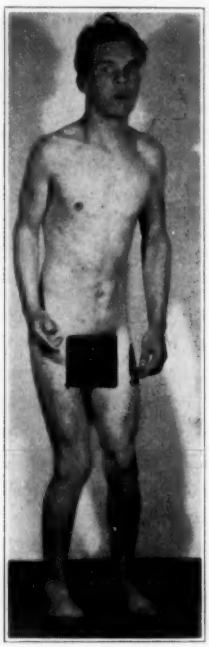
SIBLING 2.—Stanley S., a truck driver, aged 24, who was born in Massachusetts, was remarkably well developed and had never had a doctor attend him. He completed the eighth grade in school, standing well in his class. He appeared to be of average intelligence. A complete physical and neurologic examination failed to reveal evidence of disease.

SIBLING 3.—Helen S., aged 23, who was born in Massachusetts, was a slight, graceful woman who had always been well except for chickenpox as a child. She completed the eighth grade in school and graduated at the head of her class. Mentally she was very alert. A complete physical and neurologic examination revealed that she was normal.

SIBLING 4.—Benjamin S., aged 21 (figure), who was born in Massachusetts, when 8 years of age began to have difficulty in walking and also difficulty in using his right arm and hand. These conditions had grown gradually worse during the last thirteen years, and the patient could hardly walk without assistance. During the last four years there was increasing difficulty in talking. The patient went through most of the grade school and seemed to do his work with little difficulty, but during the last few years there was increasing evidence of mental deterioration. The patient had never been sick in any other way. The positive neurologic findings were: (1) masklike expression, with a tendency to drool from the open mouth; (2) dysarthria; (3) forced laughter; (4) rigidity of the facial muscles; (5) jerky movements of the eyes in looking from side to side; (6) marked rigidity of the neck; (7) rigidity of the right arm, with slight flexion at the elbow and flexion of all of the fingers; (8) tremor of the right arm and hand, which was increased when the pointing test was performed; (9) spastic weakness of the right deltoid muscle; (10) adiadokokinesis of the right hand; (11) marked adductor and flexion spasm of the legs, causing bilateral foot drop; (12) weakness of the abductors of the thighs; (13) hyperactive deep reflexes throughout, including the jaw jerk; (14) a bilateral Babinski sign, and (15) a marked scissors gait, which made walking almost impossible. The patient stood with his trunk and knees slightly flexed, and his skin showed scattered spots of leukoderma and formes frustes similar to those found in Recklinghausen's disease.

Sibling 5.—Jean S., aged 18, who was born in Massachusetts, was a heavily built girl who had always had excellent health. She went through the eighth grade in school and had good marks. Thorough physical and neurologic examinations revealed no evidences of disease.

Sibling 6.—Thomas S., aged 16, who was born in New York, was a well developed youth who had never been sick. He took an active part in the athletic life of his high school, in which he was a first year student in good academic standing. In spite of the fact that his muscular development was better than the average, he showed definite, although slight, symptoms of the disease. There was slight clumsiness when he used his hands, as was evidenced when he buttoned his



Benjamin S. Note the masklike expression and the flexion of the right arm and the legs.

clothes; he had a moderately spastic gait, and all of the deep reflexes were hyperactive. There was a slight ankle clonus on both sides, and the Babinski responses were equivocal. He tended to lose balance when he attempted to stand on his toes, but he did not realize that he had an illness.

Sibling 7.—Edna S., aged 13, who was born in New York, had experienced increasing difficulty in walking during the last three years. It was first noticed that she stubbed out the toes of her shoes. She lost balance on the slightest provocation and showed particular difficulty in walking down-stairs or down-hill. The mother thought that she was more "difficult" in later years and not so bright, but she made normal progress in school. She complained at times of sensations of "pins and needles" in the legs. Her birth and previous health record were normal. She was a little undersized. The cranial nerves were unaffected. The positive neurologic findings were: (1) moderate hypertonia of the arms, with good

power and without tremor or ataxia; (2) marked hypertonia of the lower limbs, with bilateral foot drop; (3) bilateral ankle clonus, the left being more marked than the right; (4) adductor spasm; (5) hyperactive deep reflexes throughout, those of the legs being more marked than those of the arms; (6) moderate jaw jerk; (7) positive Babinski response on both sides; (8) spastic gait with dragging of the feet, and (9) flexed posture. She had no resilience; when she jumped from the examining table this was very noticeable.

COMMENT

Familial spastic paraplegia may best be classified among heredofamilial diseases of the spinal cord group, with such conditions as familial spinal muscular atrophy (Werdnig-Hoffman disease), peroneal muscular atrophy (Charcot-Marie-Tooth disease), progressive interstitial hypertrophic neuritis and Friedreich's hereditary cerebellar ataxia. Strümpell [1] first described this condition in 1886. He believed that there were two more or less distinct groups: (1) cases which showed, clinically, rigidity of the legs, exaggerated reflexes, a positive Babinski sign and a spastic gait and, pathologically, sclerosis of the pyramidal tracts, the columns of Goll and the direct cerebellar tracts, with the onset of the disease usually between the twentieth and thirtieth years, and (2) cases which showed symptoms similar to those of the first group with the addition of mental retardation and an age of onset of from 3 to 6 years. Cases in which the symptoms are confined to these findings may be called the pure or Strümpell form of familial spastic paralysis.

Since the appearance of the first paper on this subject, 129 observers have described 150 families, some of whose members were afflicted with this disease. Rhein,[2] in 1916, reported a group of cases and at the same time made an exhaustive analysis of all of the cases reported up to that time. He believed that the various symptom complexes could be divided into seven groups: 1. The Strümpell type, i.e., cases showing weakness and spasticity of the legs, with increased reflexes and positive Babinski signs; 2. cases in which the arms are involved as well as the legs, with or without mental failure; 3. the Friedreich ataxia type, i.e., cases showing the usual symptoms plus nystagmus and scanning speech and with or without mental failure; 4. cases showing bulbar symptoms in addition to spasticity of the legs and arms; 5. the amyotrophic lateral sclerosis type, i.e., cases showing muscular atrophy; 6. the multiple sclerosis type, i.e., cases showing tremors and optic atrophy; 7. the spastic diplegia type.

Paskind and Stone [4] recently reviewed the cases reported since the appearance of Rhein's paper, and I shall make no further attempt to review the literature except to call attention to the cases reported by Litvak,[5] which were not included in Paskind and Stone's report.

Etiology.—Some observers have expressed the belief that syphilis plays a part in producing the condition, but it is striking that few cases reported in the literature show a history of syphilis. Others have attributed the disease to consanguinity of the parents. Bremer [6] declared that 20 per cent of the cases showed blood relationship between the parents or grandparents, but this alone is not sufficient to account for the disease. Whether inbreeding has anything to do with it or not, the fact must be accepted that there is some endogenous defect of the germ cell. It is noteworthy that many afflicted persons come from families which show other

5. Litvak, L. B.: Sovrem. Psikhonevrol. **8**:373, 1929.
6. Bremer, F. W.: Arch. f. Psychiat. **66**:477, 1922.

evidences of inborn deficiency—mental and physical. Among near relatives have been an extraordinary number of chronic inebriates, mental defectives, moral degenerates, epileptic persons and criminals. In Bremer's [6] exceedingly interesting report of a family comprising six generations of afflicted people, he noted and stressed a gradual degradation in the social status of the succeeding generations. In Williams' [3] series are found generation after generation of people in the lowest social order. Some German observers, notably Bremer [6] and Futer,[7] tried to show that the inheritance of familial spastic paraplegia follows the mendelian law and believed that recessive cases run a more severe course than the dominant cases which have a fairly favorable prognosis.

A few cases began to develop almost at birth, but in the vast majority of patients the disease developed normally up to a certain age. Bremer [6] came to the conclusion that 59 per cent of all cases have an onset before the eighteenth year. Five cases have been reported as developing after the age of 50. The vast majority of cases have developed insidously, although there has been a definite percentage in which an accident or a febrile disease has initiated or aggravated the illness. One must believe, therefore, that the condition is due largely to endogenous factors, but that exogenous factors do play a part. Just what these factors are, other than that there is probably a defect of the chromosomes themselves, is not known. Diseased persons undoubtedly can transmit the disease, even though the majority of cases have occurred in only one generation of a family. Apparently it is also true that the healthy children of diseased parents cannot transmit the disease to their progeny. Why the disease seems to have a predilection for the male sex, in which it occurs almost twice as often as in the female, also is not known.

Course.—The disease is as variable in development as in symptoms. It may run a rapid course, but it often develops its fullest severity in a few years and then remains stationary indefinitely. Nothing has as yet been found to have an effect in controlling its ravages.

SUMMARY

Familial spastic paralysis is a true heredofamilial degenerative disease of the central nervous system. It is perhaps the most protean of all the diseases of this group; almost any part of the nervous system may be affected. It is undoubtedly a disease primarily of the germ cell, but what more or less suddenly causes a hitherto healthy organism to degenerate in this way is not known. The pathologic changes are usually confined to the pyramidal tracts, the direct cerebellar tracts and the columns of Goll.

In this paper four new cases are reported. Three may be classified in Rhein's first category, i. e., the pure form as described by Strümpell. The fourth case, because of the combination with clinical signs indicating extrapyramidal involvement, might be called one of the parkinsonian type. Only one other group of cases of this type has been reported, that of Marinesco, Draganesco and Stoicesco.[8]

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7. Futer, D.: Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:722, 1929.
8. Marinesco, G.; Draganesco, S., and Stoicesco: Rev. neurol. **32**:1003, 1925.

SUBACUTE PRIMARY DIFFUSE ENCEPHALITIS

With Marked Involvement of the Right Central Cortical Region in a Child Aged 10

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A solution of the problem of the interrelationship of the known diseases of the central nervous system has been offered by various classifications. Spielmeyer,[1] however, commented on the difficulty of such classifications since variable changes are produced by the same irritant and similar changes are found in totally different diseases. The glial foci of simple septic endocarditis are present also in typhus fever and reach their maximum in postvaccinal encephalitis. Mesodermal intra-adventitial infiltrations are characteristic of such dissimilar diseases as diffuse dementia paralytica and epidemic encephalitis with its marked predilection for areas of inflammation. Although poliomyelitis and epidemic encephalitis affect for the most part the same regions with similar inflammatory changes, the early leukocytic infiltration of poliomyelitis and the involvement of the motor cortex are lacking in epidemic encephalitis. Dementia paralytica and multiple sclerosis show similar areas of demyelinization which are, however, not related to the so-called demyelinization of postvaccinal encephalitis but to that of postvaricella. Spielmeyer also believes that it is not possible to know whether all of the changes are produced by living toxins, since secondary symptomatic changes are similar to primary ones. Spatz [2] divided encephalitis into two forms: pseudoencephalitis and true encephalitis. In the former, the encephalitic syndrome shows no inflammatory changes. True encephalitis is therefore defined as the encephalitic reaction narrowed to all active changes in the mesodermal part of the stroma, especially those around the vessels. Spatz held, furthermore, that all true encephalitis has an infectious origin. Six types of encephalitis are presented according to the mode of their extension: (1) meningo-encephalitis; (2) metastatic foci of encephalitis; (3) diffuse polioencephalitis, a type of dementia paralytica; (4) spot-forming polioencephalitis, a type of epidemic encephalitis; (5) focus-forming demyelinization encephalitis, or acute multiple sclerosis, and (6) diffuse perivenous encephalitis, or vaccination encephalitis. This comprehensive classification serves as a guide to the recognition of the unusual forms of encephalitis

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From the Pathology Department of the Buffalo General Hospital.

1. Spielmeyer, W.: Vergleichend anatomische Betrachtungen über einige Encephalitiden, insbesondere über den Typus der Impfencephalitis, Ztschr. f. Hyg. u. Infektionskr. **113**:170, 1932.

2. Spatz, H.: Encephalitis, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 157.

that have been reported by Ossenkopp,[3] Scholz,[4] Weimann[5] and Uchiyana.[6] The case reported here also does not fall into place in the classification of Spatz.

REPORT OF A CASE

History.—A previously healthy and normal boy, aged 10, entered the Children's Hospital on Oct. 16, 1932, almost comatose after an illness of seven weeks. He was the second child of young, healthy parents. The children of the three other pregnancies were normal and healthy. The boy had never been ill except for measles three years previously. Seven weeks before admission, the child complained of headache which was relieved by lying down. The next day he appeared weak and nervous. He drooled and spoke indistinctly. A diagnosis of a nervous breakdown was made by a physician who advised complete rest except for intervals of walking. After two weeks of this treatment, during which the boy seemed to improve, he walked to the bathroom and fell into the tub, where he was found crying. He was put to bed. He slept until the following morning; when he awoke, he was unable to move his limbs or talk, but he could move his head in all directions. There was no evidence of facial paralysis. He was incontinent and swallowed with difficulty. He laughed and grimaced when spoken to. During the next five weeks he improved to the extent of being able to move his right arm and leg and his left toes and fingers.

On admission to the hospital the patient was extremely emaciated. Voluntary movements were absent, and passive movements were limited. There was loss of sensation to pain and temperature on the left side. The neck was not retracted. It was impossible to know if the child heard or understood spoken words. The deep reflexes were absent on the left side and increased on the right. The Babinski sign and the Oppenheim sign were positive on both sides. The Kernig sign was positive on the right side but negative on the left. Clonus was suggested on the left side. Convulsive movements occurred over the entire left side during intervals of two or three minutes. The pupils reacted to light and in accommodation. The ocular fundi were normal. The Wassermann reaction of the blood and spinal fluid was negative. No cells were found in the spinal fluid, but there were increased globulin, albumin and sugar. The temperature was 98 F. The breath was fetid; cervical glands were palpable.

The child did not improve. Thirteen days after admission coarse râles were heard in the lungs. The temperature, which had been gradually rising, was 108 F. at the time of death, fourteen days after admission.

Necropsy.—There were: old and fresh lobular pneumonia in the upper and lower lobes of the right lung and the lower lobe of the left; cloudy swelling of the liver and congestion of the other organs, and enlargement of the cervical, mediastinal and mesenteric lymph nodes. The brain appeared firm, with distinct surface markings. The vessels were not congested. The gray substance of the cervical cord was not sharply demarcated.

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3. Ossenkopp, G.: Paralyseartige Meningo-Encephalitis mit Diabetes Mellitus, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:380, 1930.

4. Scholz, W.: Zur Klinik- und pathologischen Anatomie der chronischen Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:533, 1923.

5. Weimann, W.: Atypische Formen der akuten Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:185, 1925.

6. Uchiyana, Tai: Pathological Studies on Encephalitis Epidemica of 1924 in Japan, Japan M. World **5**:344, 1925.

Histologic Examination of the Brain: The meninges were slightly thickened over the entire surface of the brain and were infiltrated with a few round cells. Sections from the cornu ammonis, the left central region and the frontal lobe showed similar changes. The microglia and macroglia were somewhat prominent in the molecular layer. The architectonics were not disturbed. The ganglion cells showed no Nissl substance but a faintly staining, granular cytoplasm. Ganglion cells in shadow forms and others undergoing neuronophagia by microglia were scattered through all of the layers, particularly the lower. The macroglia and oligodendroglia were not changed. The number of microglia in the cortex was slightly increased, not only in the tissue but also at the edge of the perivascular nerve tissue. The microglia consisted of normal forms and of long, slender rod cells and short, plump cells. The phagocytosing microglia in the foci

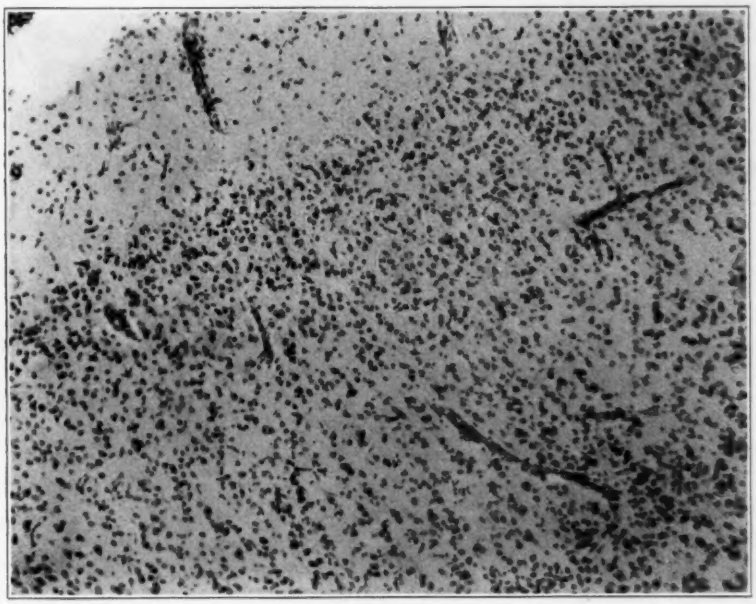

Fig. 1.—Preservation of architectonics and mild perivascular infiltration in the occipital lobe; thionine stain.

of neuronophagia were thickly spread and showed poorly staining cytoplasm. The nuclei of some of these cells were lentil-shaped; others were rounded. Vessels and capillaries showed a varying number of intra-adventitial plasma cells and lymphocytes, which formed a thin line of cuffing in a few of the larger vessels. Similarly infiltrated vessels were present in the white substance. A few microglia were found in the nerve tissue surrounding the vessels. Veins and arteries were equally infiltrated in the gray and the white substances. Neuronophagia also occurred in the ganglion cells which are present in the white substance of the brains of children.

The changes in the occipital lobe were similar to those described, except that the vessels showed a slightly more pronounced cuffing. The preservation of the architectonics and the few cells along the walls of the blood vessels can be seen

in figure 1. The macroglia of the subcortical white substance were increased in size and number.

The inflammation was more severe in the right central region than in the other parts of the central nervous system. The macroglia of the molecular layer were increased in size and number, while the microglia were numerous but not enlarged. The architectonics of the cortex were destroyed; only a few Betz cells remained, and these were undergoing chromatolysis and neuronophagia. The loss of other ganglion cells was as marked and was not confined to any layer. Macroglia with increased cytoplasm were found singly and in small glial lawns. The oligodendroglia were distended. The increase of microglia was pronounced. Many of them were of normal morphology, but a large number were long, slender rod cells. Others showed variously shaped nuclei and cell bodies, particularly

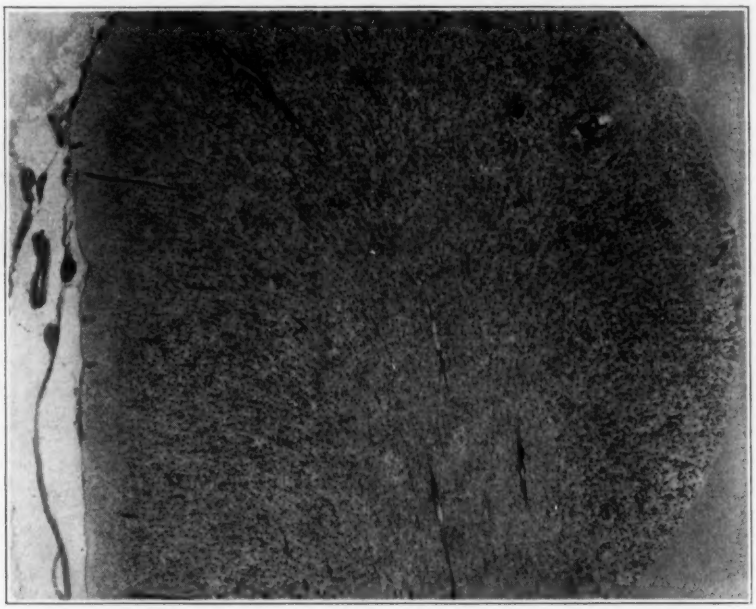

Fig. 2.—Right motor cortex showing marked perivascular infiltration and loss of architectonics and Betz cells; thionine stain.

long and short rectangular figures. The microglia in and about the destroyed ganglion cells and in the nerve tissue surrounding a few infiltrated vessels showed a varied morphology also. These cells were more plump and rounded than those scattered in the nerve tissue. As the cytoplasm of the microglia increased, it tended to take a basophilic stain, particularly in the scattered rectangular cells. Thus these cells approached the plasma cells in the morphology of both nucleus and cytoplasm. Moreover, the plasma cells were also found with the microglia, either in the nerve tissue or near phagocytosed ganglion cells and infiltrated vessels. In some round cells scattered in the nerve tissue the cytoplasm was light green, and the nucleus was small and deeply stained. It was difficult to distinguish them as oligodendroglia or as degenerating microglia. The intra-adventitial cuffing of plasma cells and lymphocytes in the vessels was pro-

nounced as shown in figure 2. Neither softening nor formation of new capillaries was observed. In the white substance the infiltration of the vessels was less marked. The vessels on the border of the gray and white substance, as well as some vessels of the white substance, presented large round cells; many of these and many of the plasma cells contained vacuoles. Astrocytes with increased cytoplasm were scattered in the white substance, chiefly in the subcortical region.

In the basal portion of the brain the perivascular infiltration was similar in intensity to that in the occipital lobe and was equally severe in the white substance, the striatum, the globus pallidus, the claustrum and the thalamus. Neuronophagia was most pronounced in the putamen. In the small periventricular nuclei, neuronophagia was more prominent than the perivascular infiltration, which was limited to a few cells around several small vessels. The only change in the cerebellum was infiltration of several small vessels in the white substance near the dentate nucleus. Slight neuronophagia and slight perivascular infiltration were observed in the substantia nigra, the red nucleus and the nucleus oculomotorius. The nuclei of the pons showed slight neuronophagia, while moderate perivascular infiltration was present around the vessels in both the gray and the white substances. Some of the veins were more heavily infiltrated than the arteries.

In the medulla oblongata there was only slight perivascular infiltration of several vessels. Neuronophagia was present in a few cells of the olives, the vagus nucleus and the nucleus trigeminus motorius. In the cervical region of the cord inflammatory changes, loss of ganglion cells or neuronophagia was not observed.

Various parts of the cortex, the basal ganglia, the medulla oblongata and the cord which had taken the myelin sheath stain did not show areas of demyelinization. However, light areas around the infiltrated blood vessels were observed in the white substance. By the van Gieson method these perivascular adventitial spaces were seen to be filled with adventitial connective tissue in which the cells were enmeshed. Bielschowsky's method showed an absence of axis-cylinders in these areas. Fat was present in large macrophages of the adventitial spaces in a few subcortical vessels, but was not found in cells of the nerve tissue. With Cajal's gold sublimate method macroglia rich in cytoplasm were observed in the cortex of the right central region. The silver carbonate stain for microglia revealed the same varied shapes that were described with the thionine stain. Repeated tests for iron gave negative results.

COMMENT

The early symptoms of the first two weeks in this case suggested the mild, abortive forms of encephalitis in children which end in recovery.[7] A short, insidious onset followed by severe symptoms is not unusual in epidemic encephalitis. Furthermore, the later course of the disease was somewhat similar to the hemiplegic encephalitic syndrome. However, the histopathologic changes showed little resemblance to epidemic encephalitis, since predilection areas of inflammation were not present in the substantia nigra or in the periventricular gray substance. The histologic and clinical observations differ from those in atypical cases of epidemic encephalitis. Weimann [5] described a case of this sort in a woman, aged 54. The illness was of four weeks' duration, but the symptoms were continually progressive. Histologic examination showed not only a diffuse perivas-

7. Zappert, J.: Der jetzige Stand der Encephalitisfrage im Kindesalter, Wien. klin. Wchnschr. **45**:737, 1932.

cular infiltration but also marked involvement of the substantia nigra and softening in the striatum and cornu ammonis. In the case of a woman, aged 43, reported by Scholz,[4] headaches and fever were early symptoms of two months' duration. A short attack of delirium and convulsions then occurred and was followed by a typical parkinsonian syndrome which lasted two years. The histopathologic changes of chronic epidemic encephalitis were present, with perivascular infiltration of the central region, loss of ganglion cells and areas of softening in the cortex and basal ganglia. The areas of softening in these two cases suggest that secondary vascular changes occur with encephalitic inflammation. These were also observed by Uchiyana[6] in epidemic encephalitis in Japan, in which hyaline changes of the vessels and areas of softening were prominent features. A diffuse perivascular infiltration of lymphocytes and plasma cells caused him to consider the inflammation as one that combined the characteristics of poliomyelitis and dementia paralytica. The clinical symptoms, however, were rapid in onset and termination.[8]

My case shows a closer resemblance to one of primary encephalitis reported by Ossenkopp[3] in a woman, aged 48, with diabetes. Early mild symptoms of six months' duration were followed by acute terminal severe ones. Diffuse perivascular infiltration of lymphocytes and plasma cells was observed in the gray and white substances of the cortex and brain stem. But the distinguishing features were marked lesions of the temporal lobe and thalamus.

The fluctuating symptoms in my case differ also from those of juvenile dementia paralytica, which is a slowly progressive disease. According to Jahnel,[9] the histopathology does not differ from that of dementia paralytica in adults, except in the involvement of the midbrain and in the accentuation of the process in the cerebellum. The latter was not present in my cases, neither were the predilection areas of inflammation in the striatum, the cornu ammonis and the frontal pole; the most intense reaction occurred in the central region, which is only lightly affected in dementia paralytica. Furthermore, the tests for iron were negative.

It is evident from the clinical symptoms and the histopathology that the case presents an unusual type of primary encephalitis. The sudden exacerbation of the symptoms after a fall in the bathtub offers the problem as to whether the child fell because of a progression of the illness or whether the fall intensified the process. The recovery of voluntary movements on the right side and the continued loss of sensation and of voluntary movements on the left side are explained by the severity of the lesion in the right central region. The terminal stage of coma suggests either an increase in the inflammation or the result of its prolongation. The entire course of the disease, however, offers no etiologic factor. A latent encephalitic virus was not apparently combined with, or incited by, an acute infection. An allergic or anaphylactic phenomenon is likewise difficult to consider. The absence of a probable etiology does not, however, present any greater problem than do other cases of encephalitis or the failure of repeated

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8. Kaneko, R.: On Epidemic Encephalitis Which Occurred in Japan in 1924, Japan Med. World **5**:237, 1925.

9. Jahnel, F.: Pathologische Anatomie der progressiven Paralyse, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, p. 417.

efforts to reproduce them experimentally, as is shown by the work of Doerr,[10] Da Fano,[11] Turnbull,[12] Spooner,[13] Eckstein[14] and Rivers.[15] Levaditi[16] reported only one case of experimental epidemic encephalitis, in a monkey which had received injections of the herpes-infected brain of a rabbit. Spontaneous encephalitis may, however, occur in monkeys, as has been reported by Bodechtel.[17]

The accumulations of microglia in the nerve tissue around some of the infiltrated vessels in the area of the most severe inflammation are like those described by Seifried and Spatz[18] in the acute phase of epidemic encephalitis, Borna disease, rabies and poliomyelitis. They are also present in distemper of dogs and in postvaccinal encephalitis, but to a much greater extent. It seems probable, therefore, that migration of microglia into the perivascular nerve tissue is part of all acute inflammations of the central nervous system. As the process continues, the perivascular microglia tend to disappear; they first disintegrate, as is shown by the cells with small, dark-stained nuclei. The plasma cells, on the other hand, become more pronounced in the nerve tissue and in the intra-adventitial spaces as the disease is prolonged.

The light areas around the vessels were similar to those of postvaccinal encephalitis which Perdrau[19] considered areas of demyelinization. If these were areas of demyelinization it seems probable that they should have become confluent at the end of nine weeks of illness. A large amount of fat should also have accumulated during this interval. However, the fat cells were confined to the subcortical vessels in the number usual in the brains of children. Therefore, the absence of fat and of merged areas suggested not only that these were not areas of demyelinization but also that the great foci of demyelinization described in

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10. Doerr, R., and Schnabel, A.: Das Virus des Herpes febrilis, Ztschr. f. Hyg. u. Infektionskr. **94**:29, 1921.

11. Da Fano, C.: Chronic or Subacute Herpetic Meningo-Encephalitis in the Rabbit, J. Path. & Bact. **30**:67, 1927.

12. Turnbull, H. M., and McIntosh, J.: Encephalomyelitis Following Vaccination, Brit. J. Exper. Path. **7**:181, 1926.

13. Spooner, E. T. C.: A Comparative Histological Study of Acute Meningo-Encephalitis Produced in Rabbits by the Viruses of Neurovaccine and Herpes Simplex, Am. J. Path. **6**:764, 1930.

14. Eckstein, A.: Klinisch-experimentelle Untersuchungen über die Vaccinationsencephalitis, Ztschr. f. Hyg. u. Infektionskr. **113**:371, 1932.

15. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**:39, 1933.

16. Levaditi, C.: Epidemic Encephalitis, Arch. Neurol. & Psychiat. **22**:767 (Oct.) 1929.

17. Bodechtel, G.: Spontanencephalitis bei einem Affen, Ztschr. f. Hyg. u. Infektionskr. **111**:331, 1930.

18. Seifried, O., and Spatz, H.: Die Ausbreitung der Encephalitischen Reaktion bei der Bornaschen Krankheit der Pferde und deren Beziehungen zur Encephalitis epidemica, zur Heine-Medinschen Krankheit und zur Lyssa des Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat, **124**:317, 1930.

19. Perdrau, J. R.: Histology of Postvaccinal Encephalitis, J. Path. & Bact. **31**:17, 1928.

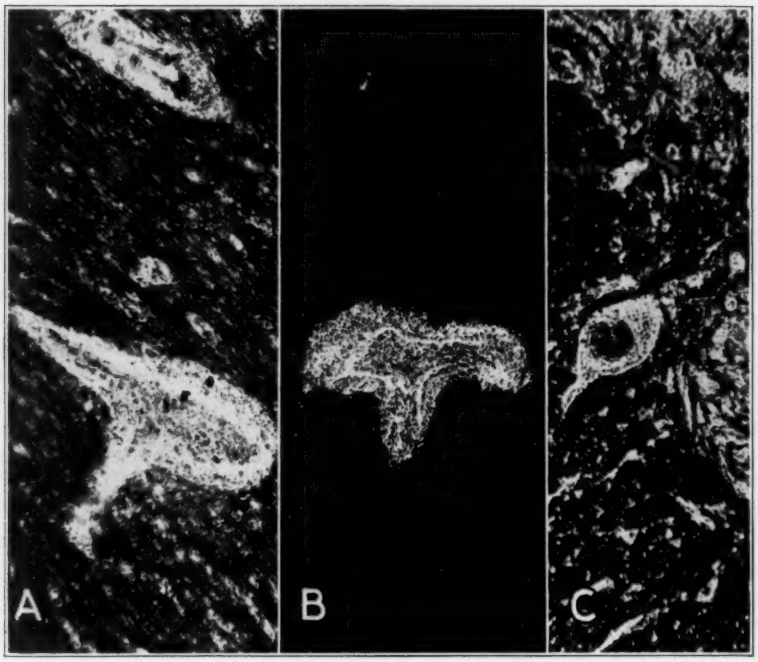

Fig. 3.—Perivascular clear spaces showing sharply demarcated line between cellular infiltration and myelin sheaths, not suggestive of demyelinization. Spielmeyer's myelin sheath stain: *A*, present case; *B*, postvaccinal encephalitis in a frozen gelatin section, and *C*, poliomyelitis.

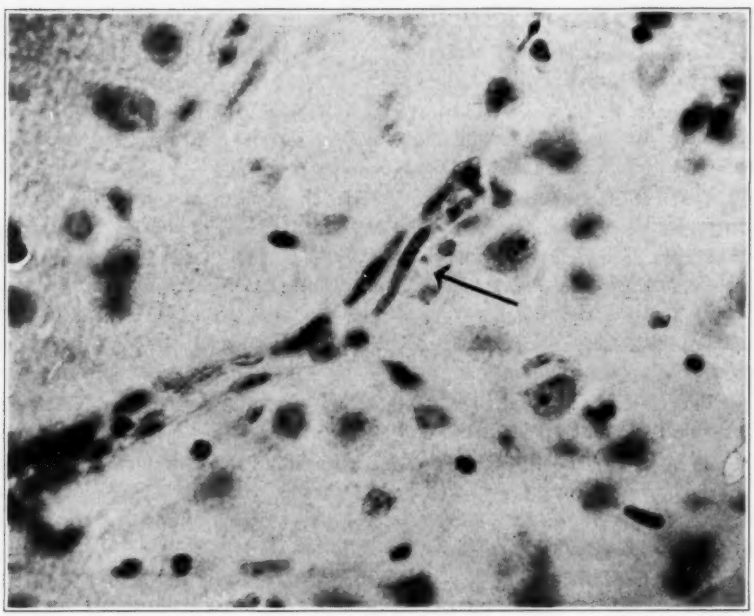

Fig. 4.—Spindle type of perivascular plasma cell, differing from the adventitial wall cell only by the deepening of the stain.

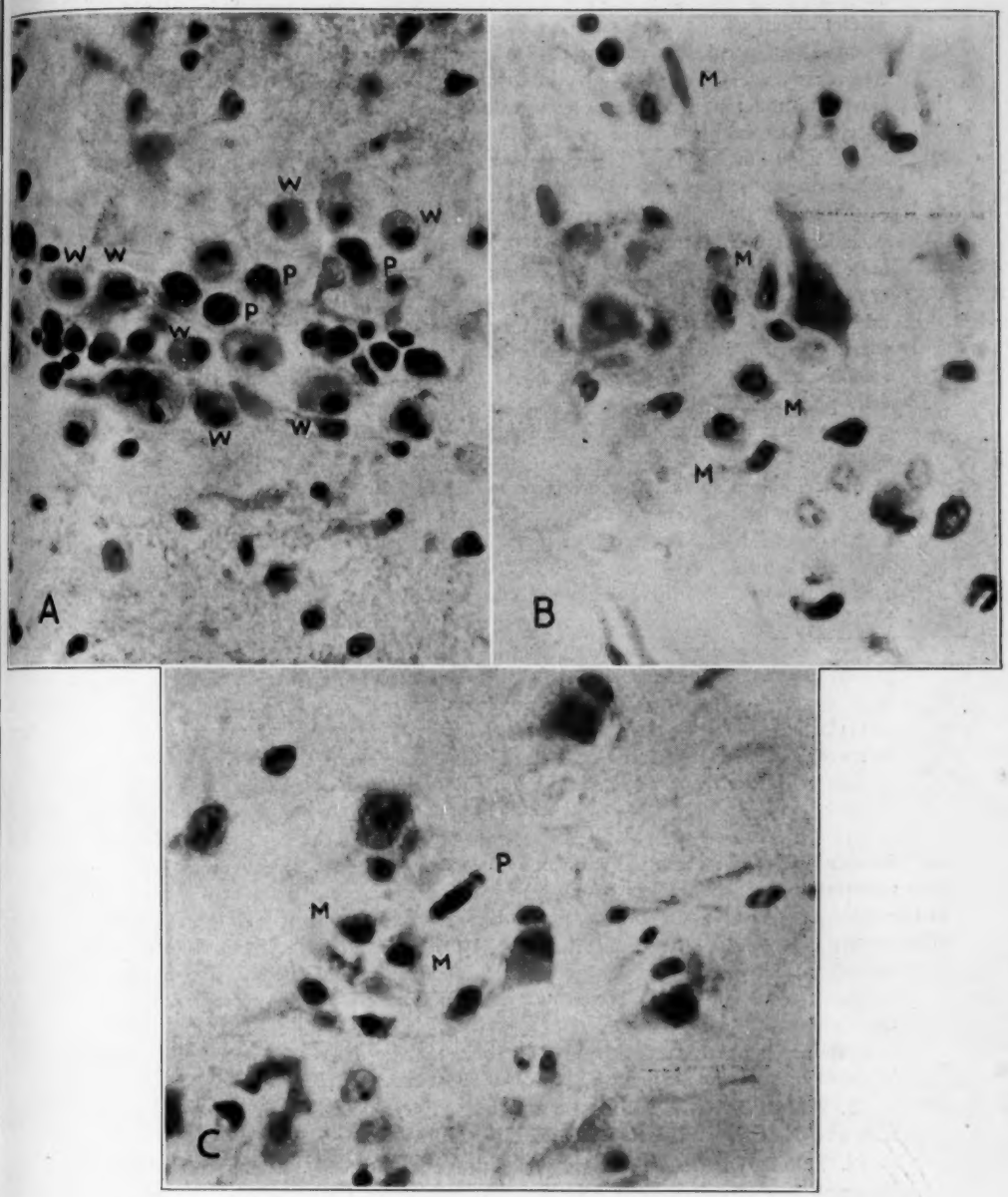

Fig. 5.—*A*, perivascular adventitial cells and plasma cells showing similar morphology; adventitial wall cells, *W*, and plasma cells, *P*; *B*, various forms of microglia, *M*, from the long, slender type to rounded types comparable with the perivascular cells of *A*, and *C*, microglia and plasma cell in old neuronophagic focus; oil immersion lens.

the late cases following varicella and measles by van Bogaert [20] and Walthard [21] did not originate from perivascular infiltrated areas. Furthermore, similar perivascular areas can also be found in poliomyelitis with Spielmeyer's stain for myelin sheaths. The similarity to the perivascular light areas in poliomyelitis, postvaccinal encephalitis and my case is shown in figure 3, in which the outlines of the vessels are followed by the infiltrating cells. If this were demyelinization, a less faithful replica might be expected. In a previously presented case of postvaccinal encephalitis [22] these areas were not believed to be due to demyelinization but to a pushing aside of the nerve fibers by the increased growth of the adventitia in the formation of new macrophages and in their need of accommodation.

Although the plasma cells are not considered phagocytes by Spielmeyer,[23] vacuoles were frequently seen in them. He also believed that plasma cells originate from lymphocytes, but the present study showed plasma cells which were similar to the various forms of adventitial wall cells in the morphology of their nuclei and cytoplasm. The spindle type of plasma cell (fig. 4) is so typical of the adventitial wall cells or pericytes that it does not seem possible that such spindle cells are formed from lymphocytes. The basophilic staining of the spindle cells and of the other forms of plasma cells suggests that this is an acquired characteristic of the adventitial wall cells, and that it is due to a different type of activity.

In a previous study [24] the origin of microglia from the spindle forms of adventitial wall cells was demonstrated. It is therefore not unexpected that the rounded and varied forms of phagocytosing microglia surrounding ganglion cells and infiltrated vessels should resemble in nucleus and cytoplasm the phagocytosing forms of intra-adventitial wall cells. Since the adventitial wall cell appears to be the origin of both the microglia and the plasma cell, an interrelation of the cells seems to follow. Such an interrelation is suggested by the presence of plasma cells with microglia in the foci of phagocytosed ganglion cells. In figure 5 is shown the similarity of the various forms of microglia, adventitial wall cells and plasma cells and their association. Figure 5 *A* demonstrates the rounded forms of both adventitial wall cells and plasma cells in the perivascular space. In figure 5 *B* the microglia have taken a rounded shape similar to the cells in *A*. In figure 5 *C* is shown the close association of the microglia and the plasma cell in the nerve tissue. Furthermore, various stages of the changes of microglia into rectangular forms with gradually deepening basophilic stain were so frequently observed in scattered cells that it can be interpreted only as the transformation of microglia into rectangular plasma cells. In figure 6 *A* the cytoplasm of the microglia is slightly thickened and of deeper stain, while in *B* both the cytoplasm and nucleus are basophilic and denote a second stage in the changing microglia, which in *C* has become a typical plasma cell of the nerve tissue.

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20. Van Bogaert, L.: Histopathologische Studie über die Encephalitis nach Windpocken, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:201, 1932.

21. Walthard, K. M.: Spätstadium einer "Encephalitis" nach Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:176, 1930.

22. Tuthill, R.: A Case of Encephalitis and Influenzal Pneumonia Following Vaccination, Arch. Neurol. & Psychiat. **24**:759 (Oct.) 1930.

23. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1932, vol. 1.

24. Tuthill, C. R., and Beck, G. M.: Reaction of Cerebral Tissue to Direct Injection of Oil, Arch. Neurol. & Psychiat. **29**:1263 (June) 1933.

Although the inflammation affects primarily mesodermal tissue, a secondary injury to the parenchyma is evident from the neuronophagia of the ganglion cells. This is also seen in the increase in size and number of the macroglia in the white substance of the occipital lobe. It is suggested that the macroglia have some other activity than that of formation of scars since neither demyelinization nor softening was observed in the occipital lobe. Moreover, a cytoplasmic rather than a fibrous increase in the glia was present. No explanation can be offered for the marked lesion in the right central region.

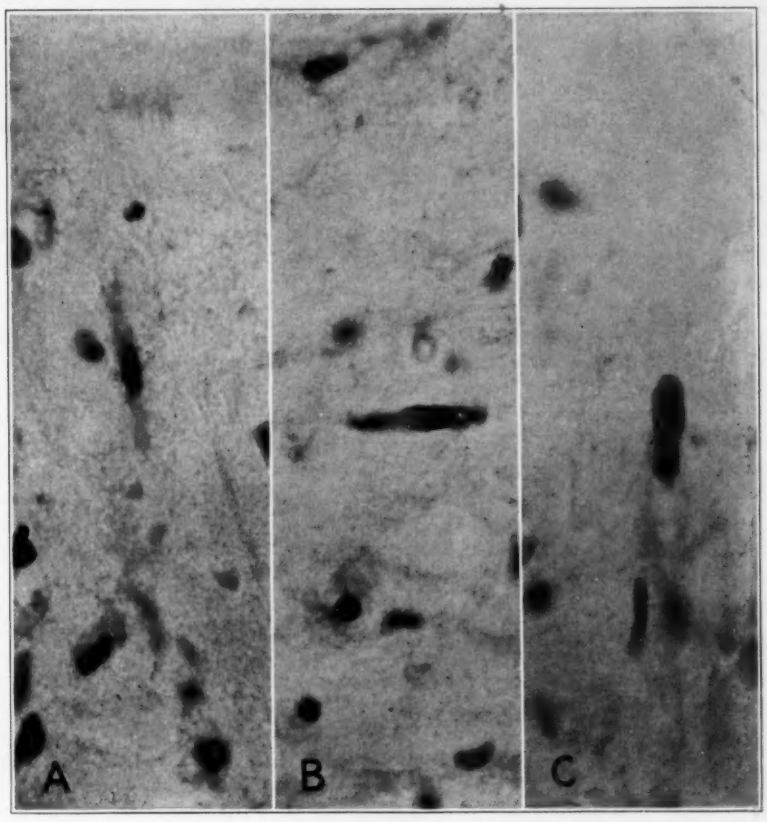

Fig. 6.—Changes of microglia, *A*, through transitional stage *B*, to plasma cell, *C*, by thickening of the cytoplasm and deepening of the stain. Thionine stain; oil immersion lens.

CONCLUSION

A case of primary encephalitis, of nine weeks' duration, is described in a boy, aged 10 years. The case does not resemble clinically or histologically either the well known types of encephalitis or the few unusual ones, and it presents a further problem in the etiology and transmission of the disease. The onset developed with sudden mild headache and weakness. After two weeks, a fall resulted in complete inability to move or speak. Gradual improvement occurred on the

right side during five weeks, when a comatose condition developed from which the child did not recover. Diffuse neuronophagia and perivascular infiltration of lymphocytes and plasma cells were present in the gray and white substance, except in the cord and cerebellum. The inflammation was most severe in the right central region, showing destruction of the architectonics and almost complete lack of Betz cells. The so-called perivascular demyelinization, such as is found in postvaccinal encephalitis, was present around the infiltrated vessels in the white substance and is considered to be adventitial overgrowth rather than demyelinization. A similarity of nuclei and of cytoplasmic forms was observed between the adventitial wall cells, the microglia and the plasma cells.

PHYSIOLOGIC MANIFESTATIONS OF EPISODIC PHENOBARBITAL INTOXICATION

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Many of the more recent studies on the barbiturates indicate that this group of agents acts primarily on the brain stem and particularly on the hypothalamic area, rather than on the cortex and other tissues. E. and J. Keeser [1] demonstrated by chemical analysis of the brains of animals killed during narcosis with barbital and dial that there is a concentration of these drugs in the thalamus and corpus striatum, whereas little or none can be detected in the cortex, medulla or cerebellum.

Pick [2] gathered the following indirect evidence that the barbiturates act chiefly on the brain stem. They produce: a retention of water; a disturbance of the heat-regulating mechanism, resulting in a fall in temperature that is often followed by fever; constriction of the pupils; increase in cardiac rate, and other symptoms of disturbance of the vegetative nervous system. He suggested that the anesthetic sleep is produced by action on the brain stem, and he laid much stress on the synergism between recognized cortical depressants, such as paraldehyde, and the drugs of the barbituric acid group. He also noted that the effectiveness of these drugs on animals was markedly increased by decortication. Magnus' [3] observations that the postural reflexes of animals became depressed by diethyl barbituric acid long before the tendon reflexes were involved suggest that the barbiturates affect the centers in the brain stem before they act on the spinal centers. Fulton and his associates [4] demonstrated that the excitability of the motor cortex of chimpanzees is little, if at all, impaired under profound anesthesia with diallyl-barbituric acid (dial-Ciba), iso-amylbarbituric acid (amytal) or sodium barbital. On the other hand, sodium ethyl (1-methylbutyl) barbiturate (pentobarbital sodium) impaired the excitability of the motor cortex. When used in full anesthetic doses, phenobarbital abolished the responses of the motor cortex to stimulation. Very large doses were used (100 mg. per kilogram), and it was found that less than this amount of the drug only partially diminished the excitability of the cortex. These

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1. Keeser, E., and Keeser, J.: Ueber die Lokalisation des Veronals im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**:251, 1927. Keeser, E.: Zur Pharmakologie der Hypnotika, Deutsche med. Wchnschr. **54**:650 (April 20) 1928.

2. Pick, E. P.: Pharmacology of Vegetative Nervous System, Arch. Neurol. & Psychiat. **23**:582 (March) 1930. Molitor, H., and Pick, E. P.: Verstärkte Schlafmittel-Wirkung durch gleichzeitige Behandlung verschiedener Hirnteile, Arch. f. exper. Path. u. Pharmakol. **115**:318, 1926.

3. Magnus, R.: Contributions to Pharmacology of Posture and of Labyrinthine Reflexes, J. Pharmacol. & Exper. Therap. **29**:35, 1926.

4. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. McK.: "Dial" as a Surgical Anaesthetic for Neurological Operations; with Observations on the Nature of Its Action, J. Pharmacol. & Exper. Therap. **40**:423, 1930. Keller, A. D., and Fulton, J. F.: The Action of Anesthetic Drugs on the Cortex of Monkeys, Am. J. Physiol. **97**:537 (June) 1931. Fulton, J. F., and Keller, A. D.: Observations on the Response of the Same Chimpanzee to Dial, Amytal and Nembutal, Used as Surgical Anesthetics, Surg., Gynec. & Obst. **54**:764 (May) 1932.

observations tend to confirm the point of view that the barbiturates act primarily on the brain stem.

In numerous papers on the toxic effects of the barbiturates only cases of acute poisoning are studied. The syndrome usually described is one of coma, often associated with vomiting, low blood pressure, pulmonary edema (usually as part of generalized edema) and fever. Most fatalities appear to have been the result of pulmonary edema. Fitch, Waters and Tatum [5] made a distinction between the barbiturates in terms of prolonged and short action. In the former group is phenobarbital, which produces death from pulmonary edema, as contrasted with the members of the latter group, which produce death from respiratory failure.

The patient on whose condition the present report is based was sent to the hospital as presenting an obscure problem of diagnosis; the possibility of addiction to phenobarbital had not been suspected. The essential clinical features consisted of somnolence, edema, diarrhea and disturbances of temperature and metabolism, all of which were in a certain relationship to each other. The constellation of symptoms suggested the presence of some sort of hypothalamic lesion.

REPORT OF CASE

History.—Mrs. J. R., a Jewish woman, aged 45, was admitted to the medical service of the New Haven Hospital on June 24, 1931, in a stuporous condition. It was reported that on the previous day she was found asleep on the floor, and that she had apparently crawled out of bed, walked to the window and crashed through it, being saved from a fall by the window-sill.

Examination.—The patient could be roused with a little difficulty; she reported that vision was blurred and that things could be seen only as shadows, that she had a bad headache and that she was very sleepy. The positive physical findings were: constricted and nonreactive pupils, divergent external strabismus, stertorous breathing, slurring speech, slight edema of the ankles and generalized muscular hypotonia. The reflexes were normal; the temperature, pulse and respiration were normal; the blood pressure was 145 systolic and 85 diastolic.

Course.—The first three days of hospitalization were characterized by a progressive decrease of somnolence, with a return to normal of the ocular and muscular signs; speech became normal, but the edema was somewhat more pronounced. There were an amputation type of anesthesia and analgesia of the left arm, with astereognosis and some muscular weakness. The patient was found to be an active, intelligent woman who took considerable interest in her surroundings. There was complete amnesia for the attack, the patient remembering events only up to the time of falling asleep.

Laboratory Findings.—The spinal fluid was normal. Examination of the blood showed: Kahn test, negative; red cells, 4,500,000; white cells, 10,300; polymorphonuclears, 44 per cent; lymphocytes, 55 per cent; smears, normal. Urinalysis revealed: appearance, clear and yellow; reaction, neutral; specific gravity, 1.006; albumin and sugar, absent; sediment, absent. Repeated gastric analysis revealed no bile or blood. During fasting the contents were: free hydrochloric acid, 0; combined, 5. Following the ingestion of 100 cc. of 7 per cent alcohol, tests showed: free hydrochloric acid, 0; combined, 10. Following the injection of 20 cc. of histamine, free hydrochloric acid was 33 and combined, 12. A series of tests of the gastro-intestinal tract following a barium sulphate meal gave negative results.

5. Fitch, R. H.; Waters, R. M., and Tatum, A. L.: Barbituric Acid Hypnotics in Surgery, Am. J. Surg. **9**:110, 1930.

Comment.—The family history disclosed that all of the grandparents had died at advanced ages, and that the parents were alive in the middle of the seventh decade. When the patient had been in the psychiatric clinic about seven months, the father died of cerebral hemorrhage. The patient was the second of six children, all of whom were active, healthy persons. She had had four children, all living and well. She had measles, scarlet fever and diphtheria before the age of 10 years, with no apparent sequelae. For a number of years she suffered from mild attacks of tonsillitis. In December, 1923, when 37, she had metrorrhagia and bilateral salpingitis; at this time hysterectomy and salpingectomy were performed. The patient seemed to be recovering uneventfully from the operation when quadriparesis suddenly developed and she had to return to bed; at this time (February, 1924), while attempting to sign some business papers, she suddenly became blind. She recovered her sight and the use of her limbs in about two months. In December, 1925, she had severe cholecystitis, and cholecystectomy was performed with uneventful recovery. In October, 1927, she underwent another operation for strangulated inguinal hernia; during convalescence another attack of quadriparesis, similar to the previous one, developed. She gradually improved, with the exception of the left arm.

Early in 1928, the patient began to suffer from periodic attacks of generalized dependent edema, which occasionally became so severe as to involve the chest and face. Edema was reported to come and go with dramatic suddenness, the patient on one occasion gaining 7.3 Kg., which was lost during about two weeks. Usually less weight was gained and lost, and its disappearance was more rapid. Altogether eight attacks of edema were reported.

In April, 1931, the patient had the first clearly recognized attack of somnolence, which lasted two or three days. Such attacks became more frequent and prolonged until the time of admission. She reported that an attack tended to come on slowly, and that she would become rather drowsy and attempt to fight it off but would invariably succumb. Before becoming comatose she became ataxic, vision became blurred and speech became thick. On recovery there was complete amnesia for events which had occurred. The headaches during and between attacks were severe. There was never any vomiting. The patient did not know whether or not there was a relationship between the somnolent attacks and the edema. The various diagnoses made in the past were atypical periodic paralysis, hysteria, polyglandular syndrome and low grade metencephalitis.

During the patient's stay in the psychiatric clinic numerous attacks of edema and somnolence were observed. It was found that a physiologic cycle of events usually occurred; the patient would begin to gain weight, and edema of the legs and arms would appear, occasionally involving the abdomen, chest and face; after from 3 to 7 Kg. was gained, in the course of from three to fourteen days, diarrhea with from five to twelve stools a day would set in (otherwise she was constipated or had one or two bowel movements a day), and after from two to five days of diarrhea she would pass into a somnolent state. There was considerable loss of weight during the periods of diarrhea. The transition from complete lucidity to profound somnolence would occupy a few hours or would be reported by the nurse as having occurred suddenly. When it occurred slowly, the patient complained of blurred vision and drowsiness; she was ataxic, and her speech was thick and slurred.

The patient was in the psychiatric clinic from July 7, 1931, to June 27, 1932. The anesthesia and paralysis disappeared suddenly in August,

1931.[6] It was not discovered until April, 1932, that she was addicted to phenobarbital, and for this reason a report concerning the amount of the drug which was ingested in most of the studies to be reported cannot be made. One study in which measured doses of from 0.3 to 0.72 Gm. of phenobarbital were given, indicates that large amounts were probably taken because of the extremely high tolerance. With experimentally controlled dosages there were produced effects of the same nature as those produced when the drug was self-ingested. The patient continually said that she did not take the drug.

The final impression was that the patient had a psychopathic personality with hysterical symptoms and episodic addiction to phenobarbital.

SPECIAL CLINICAL STUDIES

The following studies are concerned mainly with various measurements, in which comparisons of the patient's status during her normal and somnolent periods were made. The studies have been grouped under seven headings: (1) water balance, (2) cardiovascular changes (pulse and blood pressure), (3) heat regulation, (4) basal metabolism, (5) neurologic changes, (6) changes in the blood (dextrose, lactic acid, p_H) and (7) psychophysiologic changes.

1. *Water Balance.*—It was found that the patient's periodic edema could best be measured by variations in the body weight. The rapid gain and loss of weight were not accompanied by any untoward symptoms except occasional complaints of pain in the lower part of the legs, apparently due to stretching of the skin. Fluid tended to accumulate in the legs and arms and occasionally in the chest and face, the edema being of the dependent type. When the patient had hydrothorax she was somewhat dyspneic. After gaining a certain amount of weight (from 3 to 7 Kg.), fluid would be lost from the body by diarrhea (from three to twelve stools daily); there was no polyuria. The reason for the reversal of water balance is not known, except that the onset of somnolence made further ingestion of the drug temporarily impossible. With the loss of weight the patient usually went into a somnolent state, which, however, was generally terminated before the loss in weight had reached its maximum. The maximum accumulation of edematous fluid was never coincident with somnolence.

When it was discovered that the patient was ingesting phenobarbital in a clandestine manner, she was placed in strict isolation for about two months, during part of which period she was given measured quantities of the drug. Following this period, while she was still isolated as a precautionary measure, she was given no drug.

The nature of the relationship between the patient's variations in weight and the ingestion of the drug (*a*) when self-administered in presumably large doses and (*b*) when experimentally administered may be seen in charts 1 and 2, respectively. Phenobarbital was given in capsules by mouth.

(*a*) From these graphs (chart 1) it may be seen that when the drug was self-administered somnolence occurred if the patient's weight was low, i. e., when she was least edematous. Furthermore, the onset and termination of somnolence may be related to a specific relatively low threshold of edema.

(*b*) When controlled doses of phenobarbital in increasing amounts were given (chart 2), there was an increase of edema, apparently in direct proportion to the amount of the drug. With the maximum amount given (0.72 Gm.) a brief som-

6. Sears, R. R., and Cohen, L. H.: Hysterical Anesthesia, Analgesia and Astereognosis, Arch. Neurol. & Psychiat. **29**:260 (Feb.) 1933.

nolent period was also induced. Sodium amytal (1 Gm.) given intravenously apparently produced the same effect at a later date.

(*c*) When the patient was strictly isolated and no drugs were administered (from June 2 to 17), a progressive loss of edema by diarrhea, but no somnolence, was noted. Precautions in the way of isolation were extended for two months; during this time there were very little fluctuation in weight, no diarrhea and no somnolence. When the patient was again allowed complete freedom, the picture shown in chart 1 recurred, indicating that probably phenobarbital had again been ingested.

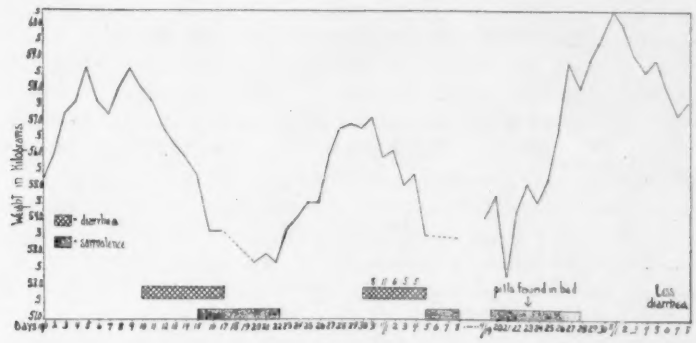

Chart 1.—Example of the cycle of edema, diarrhea and sleep which this patient produced in herself by clandestine ingestion of large amounts of phenobarbital.

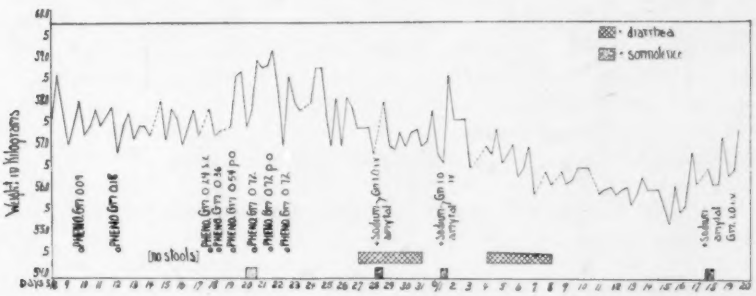

Chart 2.—Effect of large doses of phenobarbital and sodium amytal.

2. *Cardiovascular Changes.*—(*a*) Pulse: In order to discover the relationship between heart rate and the somnolent and waking periods, pulse records were taken when the patient was in both states. Pulse rates were taken over twenty-four hour periods at three hour intervals for twenty-one days; each value represents the average of twelve readings when the patient was awake and nine readings when she was somnolent, at each three hour interval. The means and their standard deviations are also presented.

It will be noted that the patient's pulse rate was faster during the afternoon and evening than in the morning when she was awake and somnolent. Furthermore, when she was somnolent, the range of variation of pulse rate was more pronounced (from 68 to 77, as against from 67 to 74 when awake). The average

difference of 2.11 beats between the two states is reliable. This finding is of interest since it indicates that the pulse rate was faster during the somnolent period. Since the patient, when awake, was physically active and when somnolent was relaxed and in bed, the significance of this difference becomes more remarkable. The tendency to a faster and more variable pulse during somnolence must therefore be admitted.

(*b*) Blood Pressure: The blood pressure was recorded over a long period of time throughout waking and somnolent periods. These data indicate that generally the systolic and diastolic pressures are lower during somnolent intervals than

Pulse Rates During a Twenty-Four Hour Period

Status	No. of Determinations	3 A.M.	6 A.M.	9 A.M.	12 A.M.	3 P.M.	6 P.M.	9 P.M.	12 M.
Awake.....	12	68	67	69	70	71	72	74	72
Somnolent....	9	70	72	68	72	70	77	77	69

		Mean	Standard Deviation	Standard Deviation, Average	Difference	Chance of True Difference, per Cent
Awake.....	97	69.8	6.38	0.65	2.11	100
Somnolent....	69	71.9	6.04	0.73		

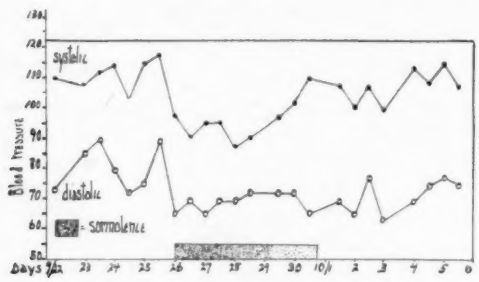

Chart 3.—Blood pressure in waking and somnolent states.

during waking ones, the pulse pressure frequently being alarmingly low. A clear-cut demonstration of changes of blood pressure during somnolence and waking is indicated in chart 3. From this graph it may be seen that not only was there a rather sudden fall of blood pressure with the onset of somnolence, but that as somnolence diminished and the patient regained her waking state, the blood pressure gradually rose. The rather sudden drop of pressure may indicate the approach to the patient's lethal dose of the drug; its gradual rise is attributable probably to the relatively slow disappearance of the toxic effects.

3. *Heat Regulation.*—In another paper [7] the diurnal variations of the cutaneous temperature of our patient and their comparison with those of five normal persons were presented and discussed. Briefly, it may be mentioned that cutaneous temperature readings with a thermocouple and galvanometer were made over twenty-four hour periods every three hours for twenty-eight days, beginning during a

7. Heiser, F., and Cohen, L. H.: Diurnal Variations of Skin Temperature, J. Indust. Hyg. **15**:243 (July) 1933.

somnolent state and ending as the patient was waking from another somnolent state. Measurements of the temperature of the mouth, forehead, neck over the left carotid artery, wrists and ankles were made. In that investigation it was found that during somnolence the patient's oral temperature was higher than when waking, but lower than the average of the control group. On the other hand, the temperature of the forehead was higher during the waking state than during somnolence but lower than that of the control subjects. The temperature of the neck was lower for our patient than for the controls; the temperature of the left and right wrists and ankles was slightly higher during somnolence and close to the average of the control group. A more important finding, however, was that the diurnal range of temperature variation during the somnolent state was much smaller and more irregular than that during the waking state, indicating that during somnolence there was a weakening of the normal temperature rhythm. From these data, therefore, it may be seen that during somnolence there occurred some disturbance of heat regulation in which there was a disturbance of temperature level and of normal temperature variation.

4. *Basal Metabolism.*—Basal metabolic rates were obtained with the Benedict-Roth apparatus and recorded according to the standards of Aub and DuBois. These were obtained under two sets of conditions: (1) at 9:30 a. m. on various days over a period of almost four months, including waking and somnolent days; (2) every three hours during a somnolent day and a waking day. The data of (2) are not included within (1). The basal metabolic rate was obtained on twenty-four different days, of which seventeen were waking and seven somnolent days. The widest range of variation was found during somnolence: —33 per cent on one morning and + 6 on another. The mean basal metabolic rate for the waking and somnolent days was —15 per cent. However, the mean variation for the basal metabolic rates on waking days was ±4.3 and for the somnolent ±8.0, indicating greater variability of metabolic rate under the latter conditions.

Over the twenty-four hour period during which the metabolism tests were taken the patient was given nothing except water and orange juice. It was found that the patient's mean basal metabolic rate was —13 per cent during wakefulness and —11 per cent during somnolence. This difference is probably not reliable, but indicates a slight, though perhaps not significant, diminution of basal metabolism during somnolence. A more interesting observation, however, was that the average mean variation of the basal metabolic rates during waking hours was ±4.2 per cent and during sleep, ±8.6 per cent, again indicating the greater variability of metabolic rate during somnolence.

5. *Neurologic Changes.*—The principal neurologic characteristics of the patient's waking and somnolent states were: When she was waking, there were no particular abnormalities detectable except a dry, scaly skin which had been diagnosed as seborrheic dermatitis. She occasionally complained of dyspnea when there was fluid in the chest and of pain over the ankles when they were edematous. Occasionally before, and always after, a somnolent period she complained of blurring of vision. When somnolent, the patient had bradypnea; markedly constricted pupils, which did not react to light or in accommodation, the eyeballs deviating upward and slightly outward; thick and slurring speech, and muscular flaccidity of the head, trunk and extremities. The pupillary changes and strabismus were the first to appear and the last to disappear. She invariably complained of headache during and for some time after the somnolent periods. Despite the generalized muscular flaccidity, the deep reflexes were active. The absence of free hydrochloric acid in the stomach has previously been mentioned. It was most difficult

to rouse the patient when somnolence first supervened and progressively less difficult as the days went on.

6. *Changes in the Blood.*—Altogether eight determinations of blood sugar were obtained—five when the patient was awake and three when somnolent. When she was awake the mean blood sugar level was 73.7 mg. per hundred cubic centimeters (range, from 65.8 to 83 mg.; mean variation, —4.25); when somnolent, 74.3 mg. per hundred cubic centimeters (range, from 71 to 77 mg.; mean variation, ±2.23). These data, though limited, indicate that no significant change in blood sugar level occurred when the patient was in a somnolent condition.

The lactic acid and the p_H of the blood were studied on occasions when the patient was somnolent and awake. It was found that when the patient awoke from the somnolent state there was little change in the lactic acid content, but that the p_H [8] rose markedly from 7.25 to 7.36. The p_H of 7.25, obtained during deepest somnolence, indicates severe acidosis. The significance of the acidosis in the production of other findings cannot be evaluated by us at present.

6. *Psychophysiologic Changes.*—Some psychophysiologic and psychologic aspects of the patient's status will be presented in another paper [9] in which her efficiency in acts demanding activity of the central nervous system was studied during wakefulness and somnolence. The studies included excitability of the patellar reflex, reaction time to sound, conditioned finger retraction to sound, simple attention maintenance, rhythmic response to patterned sound stimuli, rote memory for digits and unconnected words and fluidity of free association. The various data demonstrated that although there was a depression of the efficiency of the central nervous system, including the so-called higher functions, the degree of disturbance was less pronounced the higher the level of the activity demanded of the nervous system.

The patient was followed after discharge from the clinic. When last seen in June, 1933, she was much improved and was happy. All of her children had grown up and had been successful; all except one were married. She had separated from her husband, who had been a great trial to her, and was receiving a great deal of attention from a man whom she admired very much. There were no serious economic problems because she received an income from her father's estate. She stated that she had not had any more sleeping spells or edema, and her sister corroborated this point. She was even willing to admit that the phenobarbital which she used to take might have had something to do with the sleeping spells, and stated that she had not taken the drug since leaving the hospital.

Thus it appears that relief from the numerous difficult problems and responsibilities made it possible for the patient to give up her hysterical symptoms, as well as the ingestion of phenobarbital, and to make an excellent recovery. It looks as if she will remain well as long as life continues to be pleasant for her.

COMMENT AND SUMMARY

The history and clinical findings indicate that in a patient addicted to the ingestion of large doses (at least 2 Gm. daily) of phenobarbital there is a severe disturbance of the autonomic nervous system. The functions attributed to the cerebral cortex, especially the more complex ones, are relatively little impaired. The findings of disturbed water metabolism, somnolence, increased and more

8. Dr. H. E. Himwich of the Department of Physiology made these determinations.

9. To be published.

variable pulse rate, disturbance in temperature, variations in basal metabolism and neurologic changes of muscular flaccidity, with little disturbance of reflexes, seem to point to dysfunction of the brain stem and particularly to that of the hypothalamic region. The relatively less impaired cerebral functions suggest that the site of action is not, at least so importantly, cortical. The constellation of these clinical findings argues that there may be a common center for them, and that this region is the major locus of disturbance in intoxication due to phenobarbital.

PRIAPISM OF PSYCHOGENIC ORIGIN

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Scientific interest in the psychic factors associated with priapism is of recent date. Cases of priapism which could not be attributed to any of the many common causes for priapism, such as trauma to the cord, leukemia and local irritations, were grouped as idiopathic. Among the so-called idiopathic cases one can discern psychic factors which might account for the condition, but which were rarely emphasized by the observers. Even writers of the psychoanalytic school who have delved so extensively and deeply into the psychogenesis of physical manifestations have little to say on the subject. The following case, therefore, seems worthy of note.

REPORT OF A CASE

A well built, apparently physically healthy Negro, aged 22, from Santo Domingo, was admitted to the genito-urinary service of Mount Sinai Hospital, New York, on July 2, 1931, suffering from priapism. The condition had existed for about sixteen hours prior to admission and was painful. In the surgical ward applications of cold, wet dressings and sedatives were unsuccessful. Caudal anesthesia (procaine hydrochloride, 1 cc.) administered fourteen hours after admission did not bring relief. The corpora cavernosa were then tapped with large bone needles, resulting in transient relief from the priapism. On July 6, avertin anesthesia (6 cc.) proved ineffective. As a result of psychiatric examination he was transferred to the neurologic service. The local application of an antiphlogistic, cold compresses, ice-bags and the administration of sedatives, such as bromides, had no effect. Attempts at hypnotizing the patient were also unsuccessful. He was then placed in a continuous bath for many hours each day for three weeks, and after thirty-six days the priapism gradually disappeared.

In the genito-urinary ward no local conditions were discovered which could account for the priapism. The inguinal glands showed marked enlargement; the epitrochlear glands were palpable, the penis was erect, and spasm of both ischiocavernosi was present. Neurologic examination revealed no abnormalities. The general physical examination showed a normal condition. The Wassermann reaction and colloidal gold test of the spinal fluid were negative; the urine was normal. A blood count showed sickle cell anemia, with 2,800,000 red cells, practically all of which were sickle cells; the hemoglobin was 55 per cent. Examination of a stool showed infestation with Trichocephalus dispar. The serologist, clinical pathologists and general medical consultants were of the opinion that the sickle cell anemia and the intestinal parasite, both of which are common in the West Indies, were not responsible for the priapism.

The psychosexual history in the case, however, disclosed what appears to be a definite psychic cause for the priapism. The patient was born in the family of a working man in Santo Domingo. He had had five brothers and six sisters; only two sisters, both older than the patient, were living. The mother was a strict disciplinarian who insisted on proper conduct. The patient had elementary schooling and was sufficiently intelligent to cooperate in the essentials of a psychiatric

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examination, but the facts were obtained with some difficulty because of his limited command of English. He was an unskilled worker, industrious and conscientious when he had employment.

For the psychogenic interpretation of the patient's symptom, the principal concern is with a sister, twelve years older than the patient. The patient's mother, as well as the father, went to work, so that the patient was brought up by this already mature sister who acted as a mother to him from the time he was weaned until she came to the United States when the patient was 9 years of age. From that time on he slept in the same bed with his mother until the age of 16. He could give no satisfactory reason why the father and mother did not sleep together. The mother "just wanted it that way."

The patient began to masturbate at the age of 8, indulging daily for about ten minutes and endeavoring to continue the erection as long as possible. At the age of 15 he began coitus with prostitutes, but refrained from ejaculating intravaginally because he had heard that ejaculation intravaginally predisposed to the contraction of venereal disease. He took pleasure in continuing coitus for fifteen or twenty minutes without losing the erection. After he left the scene of intercourse he would walk about the streets for from ten to twenty minutes, when he would experience a spontaneous ejaculation.

He realized that his sexual approach deviated from the normal, for he experienced no desire to kiss or caress a woman. This often aroused their resentment. He took especial delight in their disappointment at his failure to ejaculate. Moreover, the desire to urinate caused an erection, and at times a prolonged erection would be relieved through urination. At the age of 18 he had what appears to have been the first semblance of a love affair with a girl of his own age, with whom he practiced coitus and ejaculatio frustrata. Except on a few occasions ejaculation occurred from ten to twenty minutes later, away from the scene of the coitus.

The patient's sister, who had emigrated to New York when the patient was still a boy, had married, but on the death of her husband she returned to Santo Domingo to fetch the patient, then aged 20, to live with her in New York. She was a comely, colored woman, aged 32. In New York the patient lived in her room, where they slept in the same bed continuously until the patient entered the hospital a year and a half later. The sister warned him that the sexual freedom which he had enjoyed in Santo Domingo could not be pursued with impunity in the United States. The patient considered his sister's moral code even stricter than that of his mother. However, he was induced to go to a house of prostitution shortly after his arrival in New York, and the house was raided by the police while he was present. Although he was not in any way molested, he claimed that he became so frightened that until the occurrence of the priapism about a year later he discontinued any further attempts at coitus except on one occasion. About two months before the onset of the priapism he succeeded in having his first intravaginal ejaculation after about one hour of coitus with a woman who was not a prostitute.

In an interview the sister stated that she had acted like a mother to him and that although they had occupied the same bed she took precautions to go to bed early, and her brother did not retire until very late at night. However, in her account she made a slip of the tongue, saying, "my hus . . . I mean my brother always comes to bed late."

On the other hand, the patient stated that for two months prior to admission to the hospital he had been troubled with nocturnal erections which he found impos-

sible to relieve. He would usually rise from bed about 3 a. m. and walk the streets for from two to three hours, after which the erection would disappear without ejaculation, and he would return home to sleep. The patient would often arise late in the morning, about 11 to find that erection had reappeared. He would again resort to walking as a cure and spend the time from 11 a. m. to 4 or 6 p. m. in walking off the erection. If walking failed, occasional urination would relieve the condition. Two nights preceding admission to the hospital the usual phenomena had occurred, but on this occasion the customary remedial procedure failed, and priapism continued until he entered the hospital.

After cessation of the priapism, the patient found that he had lost the power of erection, although he exposed himself to sexual contact on several occasions. He did not resume sleeping with his sister, because he said that as a result of the resident physician's admonition in the hospital he thought that such intimate contact was wrong. After trying intercourse several times unsuccessfully, he heard of a colored woman with a reputation for infallibility in overcoming such conditions as the one with which he was afflicted. This woman, however, did not succeed in inducing an erection, but infected the patient with gonorrhea about October, 1931. He was under treatment for urethritis in the outpatient department of the hospital until February, 1932. When he recovered he returned to sleep in the same bed with his sister, but claimed that his body never touched hers. Erections no longer occurred in her presence. As the only approximation to normal sexuality had occurred with the girl with whom he had a love affair at the age of 18, it was suggested that he force fantasies of the scenes he had experienced with this girl. Attempts at such forced fantasies produced only weak and transient erections.

Although the patient had been advised to occupy different sleeping quarters from his sister he did not do so until September, 1932. During the period from February, 1932, until December, 1932, he experienced erections in masturbation, but did not attempt intercourse. In December, 1932, he attempted intercourse; erection occurred slowly, and ejaculations were retarded for from fifteen to twenty minutes. He claimed that he now never experienced erections except when actually in contact with women.

During an interview in May, 1933, he stated that he had been indulging in intercourse about once a month. Ejaculations still came slowly, but not to the extent prior to the priapism. He felt that in his approach to women his attitude was far less morbid than previously. On July 1, about two years after the priapism, the patient was living in a room by himself. He was indulging in intercourse irregularly, but had returned to masturbation two or three times a week. He claimed that he had reverted to this practice because of fear of incomplete erections. He claimed that even in masturbation erections were not complete. His general physical condition was excellent. Examination of the stool revealed no parasites, and examination of the blood showed the presence of sickle cells with no caps.

COMMENT

The case reported is considered to be one of priapism because the erection lasted continuously for over a month, was painful and was unaccompanied by sexual desire. The reasons for considering it of psychogenic origin are: (1) the exclusion of any known physical cause for the priapism by physical examinations done by competent specialists in the various fields of possibility and by extensive laboratory investigations; (2) the existence of abnormality in the patient's sexual practices of long standing, indicating a preparation for the final development of the symptom of priapism. The psychogenic mechanism is construed as being

dependent on an unconscious desire for sexual relationship with his sister, which involuntarily produced the erection. Any satisfaction of the desire was inhibited by a partially conscious or even unconscious desire to avoid incest. The development of the priapism had undoubtedly been facilitated by the conscious prolongation of erections by the patient in masturbation and in intercourse over a period of ten years.

In discussing the psychogenic factors in priapism it becomes necessary to define the term. In some of the so-called idiopathic cases it is questionable whether the condition is not merely one of prolonged erection, recurrent nocturnal erection or continuous sexual excitement embraced in the general category of satyriasis. These manifestations are usually transitory and are apt to subside after intercourse or spontaneously.

The term priapism should be restricted to a condition of persistent and prolonged erection, painful as a rule, unaccompanied by sexual desire and not relieved by sexual intercourse. Prolonged erections accompanied by sexual desire, when ejaculation for one reason or another is inhibited, are common. They are found particularly in masturbatio frustrata, in which the patient avoids ejaculation because of the undue value which he attaches to the loss of semen. One of my patients suffered from erections which he could continue intravaginally for from two to three hours, but these priapismic erections, which were quite painful, were unaccompanied by any conscious sexual desire. Another patient, who also suffered from ejaculatio retardata, induced painful erections which would last from twenty minutes to half an hour by standing nude in front of a mirror and smoking a cigaret. Disturbances such as ejaculatio retardata and ejaculatio frustrata, which are met frequently by those treating psychologic sexual disorders, are not usually included under the general category of priapism. They are manifestations allied to ejaculatio praecox, the origin of which can be traced to the unconscious impulse to injure or retaliate on the sexual partner. In the case reported here the patient was so aware of the punitive purpose of the action that originally the prolongation of the erection was intentional.

The number of cases of priapism from any cause recorded in the literature is not large. The résumé of Frank Hinman,[1] in 1914, contained 170 cases, and in 1929 McKay and Colston[2] added 22 cases. Including several additional scattered reports there probably have been reported approximately 200 cases. An excellent monograph on priapism by Bruno Cohn,[3] published in 1920, covers the accepted classifications of priapism and in addition calls attention to the so-called idiopathic cases which do not fall under any of the headings proposed by Terrier, Victor Blum or Scheuer. Gobel, quoted by Cohn, in 1904, reported 10 cases of idiopathic protracted priapism, but subsequent authors were not convinced that all these cases were not due to some organic disorder. In neither of the 2 cases reported by Cohn as idiopathic was the investigation of the patient's psychic life extensive. On the other hand, a case reported by Mainzer[4] indicates the existence of psychic inhibition dependent on external circumstances. Mainzer explained the priapism on the fact that the patient's wife had been forbidden to conceive and the patient was too poor to purchase contraceptives.

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1. Hinman, Frank: Priapism, Ann. Surg. **60**:689, 1914.

2. McKay, R. W., and Colston, J. A. C.: Priapism (A New Method of Treatment), J. Urol. **19**:121, 1928.

3. Cohn, Bruno: Zur Frage des idiopathischen Priapismus, Thesis, Berlin, July, 1920.

4. Mainzer, quoted by Cohn.[3]

In 1917, Wolbarst [5] reported a case of prolonged erection in a young man studying for the priesthood, in whom the conflict between the unconscious desire for sexuality and conscious inhibition was held accountable for the condition. In discussing Wolbarst's case, A. A. Brill added 4 cases of priapism in which he stressed certain unconscious homosexual and exhibitionistic elements as being responsible for the condition. The description of Brill's cases, however, is not sufficiently detailed positively to establish the psychogenic factors or to warrant their inclusion under the term priapism as I have defined it.

In the case reported by Stekel [6] nocturnal priapism disappeared in the morning, and one may still doubt whether the priapism was anything more than prolonged, unrelieved, conscious sexual excitement. So far as I know, no case of priapism subjected to extensive psychoanalytic investigation has yet been recorded.

The most convincing instance of psychogenic priapism is one reported by Dukeman.[7] At the time of observation the patient had suffered from persistent priapism for five months and previously at intervals for months at a time. The patient's father was an officer in the English army, stationed in the south seas. The patient at the age of 7 was stolen by natives and was not returned for four years. During that time he was used as an idol by the natives, who practiced fellatio with him as part of their religious ritual or perhaps also to satisfy sexual desires. A state of chronic erection began to appear in the boy. He would often have violent spasms of the penis, lasting for several days, which were relieved only by performing fellatio on himself. The patient married at the age of 16 and became the father of three children. He was free from priapism until after the death of his wife, when the difficulty returned.

In the case reported here the failure of the patient to regain the power of erection after the prolonged priapism might lay open to question the psychogenic origin of the disorder. Indeed, reports of impotence following priapism are not infrequent. McKay and Colston claimed that after forty-eight hours of persistent erection, no matter what the cause is, certain local changes are produced which interfere with effective treatment. Such changes may possibly have an influence in the production of subsequent impotence. However, the view of McKay and Colston has not been proved, and other observers argue to the contrary.

In the case reported here, no symptom in the acute phase of the priapism developed which might be construed to indicate an obscure organic basis for the subsequent weak potency. On the other hand, in cases of prolonged erection and hyperpotency in which psychogenic factors are unquestionably the cause, these conditions have alternated with impotence. The same psychogenic mechanism which often motivates ejaculatio praecox and ejaculatio retardata may be responsible for a condition simulating priapism. In each instance the unconscious motive is the disappointment, deprivation and frustration of the woman. From the woman's angle, ejaculatio retardata usually proves to be not only a disillusionment similar to ejaculatio ante portas, but an extremely painful and irritating experience, physiologically as well as psychologically. In the consciousness of the male the same humiliation at his failure exists, but investigation of the unconscious indicates that in each instance a deep and powerful hostility to the female dominates the delayed physiologic response.

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5. Wolbarst, A. L.: A Case of Persistent Priapism, M. Rec. **91**:542 (March 31) 1917.

6. Stekel, William: Ztschr. f. Sexualwissensch. **5**:272, 1918.

7. Dukeman, W. H.: A Case of Priapism of Several Years' Duration, Pacific M. J. **32**:420, 1889.

Abstracts from Current Literature

CEPHALIC ZONAS. J. REBATTU, P. MOUNIER-KUHN, J. DECHAUME, P. BONNET and A. COLRAT, Rev. d'oto-neuro-opht. **11**:241 (April) 1933. (An abstract of the second part of this article appeared in the May issue, p. 1100.)

The subject of cephalic zona is discussed exhaustively and occupies two entire numbers of the *Revue*. Today, zona is no longer considered as a lesion localized in a single cerebrospinal ganglion. Furthermore, the cutaneous manifestations may fade into the background, and motor paralysis may dominate the scene. At times a clinical syndrome occurs which points to an attack on the neuraxis, not only spinal but also cerebral. Zonas of the head may be: (1) those with a sole or principal location in the cranial nerves possessing a ganglion (including here zonas localized in the first three cervical roots, which supply the neck); (2) aberrant sensory, motor or cutaneous cranial nerve manifestations in the course of zonas of the trunk or limbs; (3) clinical syndromes that indicate an attack on the brain itself by the zonal virus.

The viruses of zona and of herpes are related, but are sufficiently unlike to justify an etiologic differentiation. The question of the identity of the virus of zona with that of varicella is still debated. Numerous investigations have failed to identify or transmit the virus of zona, but it may be assumed that zona is a specific infectious disease, very slightly contagious, and that the virus belongs to the filter-passing group. The nerve lesions involve the sensory pathways, especially at the level of the nerve cell in the sensory ganglion, along which they may extend into the dendrites and the axis-cylinder. They may involve even the second cellular relay, either in the posterior horns of the cord or in the bulbar sensory nuclei. Aside from the lesions of wallerian degeneration in the nerves and in their bulbomedullary roots, primary lesions of the sensory ganglion, the nerves, their roots and the bulbar nuclei may be caused by zona.

Some years ago, it was assumed that the pathogenic agent in zona was localized in the spinal ganglion, where it attacked the sensory, vasomotor and trophic fibers. Today the exclusively trophic nature of the cutaneous or ocular lesions cannot be maintained. Zona is always due to a specific agent, and if certain zonal eruptions are symptomatic it is because they are localized in radicular territory that has been prepared by some other disease. The inflammatory process is not only ganglionic, but is also ectodermic and nervous—aneurotropic ectodermosis; it is really a septineuritis, with affinity of the virus for the sensory neuron. In its generalized form zona is allied to the eruptive fevers and is a transition between general infections (especially dermotropic) and neurotropic infections.

Two modes of inoculation have been postulated: the exogenous (Marinesco) and the endogenous (Levaditi). In the former, the virus attacks first the epidermal cells and then follows along preformed pathways (spaces between the nerve bundles) to the ganglion or cord when the eruption occurs. In the latter, reservoirs of virus in the pharyngeal mucosa and tonsil crypts are assumed. Under the influence of cold, generalized infections or other factors, the microorganism enters the circulation and becomes fixed in the neuro-ectodermic tissues.

Common complications are paralysis, postzosterian pains and trophic disorders. The virus affects the motor neuron by compression by the ganglionic lesions, by extension of the inflammation from the ganglion to the motor neuron, by passage of the virus along the anastomoses between the motor and sensory nerves or by propagation of the lesions of the gray substance of the neuraxis to the anterior horn (nuclear origin). In cephalic zona it is a question whether the postzosterian pains are due to involvement of the gasserian ganglion or of the bulbar nuclei, the former being characterized by paroxysmal attacks resembling causalgia and the latter by lightning-like pains and vasomotor disturbances.

Arguments in favor of a sympathetic origin of postzosterian pains are: painful phenomena during lesions of certain sympathetic ganglia and the normal inhibiting action of the sympathetic on sensibility. The sympathetic is involved in herpes zoster, especially cephalic zonas, and this probably plays a part in the production of the pains. Trophic disturbances are of sympathetic origin. Jonnesco showed that, in syringobulbia, trophic and sensory troubles follow a parallel course and are located in the same territory. If trophic disturbances indicate involvement of the neurovegetative system, the relations, not only in the bulb but throughout the body, between the sensory pathways and the neurovegetative system must be very close.

Exclusively motor cranial nerves are not primarily attacked by the virus of zona, but may be paralyzed secondarily. The same is true of the optic and olfactory nerves. The mixed motor and sensory nerves have an organovegetative component: They either contain sympathetic fibers or have near their motor centers a neurovegetative nucleus. They are the homologs of the spinal nerves and may be the seat of the primary manifestation of zona.

Infectious manifestations in cephalic zona are almost constant, but they are not marked. Fever is frequent in patients under 30 years of age, but is of short duration; mild digestive disorders, lack of appetite, somnolence and chilliness are often observed. These general symptoms soon pass into the stage of violent pains. Adenitis is almost constant and is in relation with the skin lesions. Hyperleukocytosis, with eosinophilia and polynucleosis, appears during the first few days, disappears and then returns during desquamation. In varicella there is leukopenia with mononucleosis. The occurrence of zonal meningitis is undoubted. Usually it is slight and transient; at times it is localized, although Eschbach observed a grave generalized meningitis that lasted six months, but there were apyrexia and lymphocytosis of the spinal fluid. Lumbar puncture is often the only means of discovery. Cytology shows a marked cellular reaction, up to 100 or 200 elements per cubic millimeter (Nageotte), albuminorrhachia is generally increased and glycorrhachia has been observed. The Bordet-Wassermann reaction is negative and that with colloidal benzoin approaches the meningitic formula.

Clinically, zonal paralyses are well known, but their pathologic interpretation is obscure. Ocular paralyses are, as a rule, observed only when the ophthalmic nerve is involved and are unilateral. Certain paralyses are unperceived by reason of their transitory nature and the presence of inflammatory ptosis. They occur from five to seven days after the eruption. The common motor oculi is most often involved. The paralysis may be total or partial, and all combinations are seen. The superior and inferior rectus muscles are seldom solely involved. The internal ocular musculature is habitually affected at the same time. In typical cases the pupil is dilated and reacts neither to light nor in accommodation. The unilateral Argyll Robertson sign has been observed; trophic disturbances of the iris explain the phenomenon. There is a strong tendency toward recovery from the paralysis after two or three months. Their pathogenesis is obscure, probably being sometimes peripheral, sometimes central. In the former case, the summit of the orbit where the branches of the ophthalmic and the motor nerves are near together is supposed to be the place at which transfer of the virus from one to the other occurs. Charcot's hypothesis of a central lesion involving the nuclei of origin was adopted by Brissaud who, in 3 cases of ophthalmic zona with ocular paralysis, followed by alternate hemiplegia, assumed a single lesion situated at the foot of the peduncle and embracing the termination of the ascending root of the trigeminus, the nuclei of origin of the third nerve, the pyramidal bundle and the ribbon of Reil. No observations at autopsy supported this view. In cases of sole involvement of the internal musculature, it is probable that a single lesion of the ophthalmic ganglion existed.

Facial paralysis is common in cephalic zona. Ramsay Hunt found it 12 times in the course of otic zona, 12 times in zona of the face, 32 times in occipitocervical zona and 3 times in zona of the face and neck. The authors observed

facial paralysis 152 times in a total of 267 observations in cephalic zona, among which, however, there were only a few cases of ophthalmic zona. It usually occurs from three to five days after the eruption appears; it may appear before the eruption or, more rarely, coincident with it. The type is peripheral, the seat is on the side of the eruption, and the paralysis is usually preceded by prodromes, though it may be complete from the beginning.

The principal theories of the pathogenesis of zonal facial paralysis are: the peripheral theory, developed by Head and Campbell and Ramsay Hunt, the meningeal theory (Brissaud and Souques) and the theory of direct attacks on the motor nuclei in the neuraxis (Claude and Schaeffer). According to the peripheral theory, the nerve may be compressed by swelling of the ganglion (mechanical theory), or it may be directly involved by contiguity or by way of anatsomoses between the facial and the geniculate ganglion, or between the acoustic and the intermediary nerves of Wrisberg (infectious theory). Probably the pathway varies with the case: When the paralysis is transient the lesion is peripheral, and when it is definitive or of long duration the motor nuclei are involved. Only 3 reports were found in the literature in which a zonal facial paralysis had been followed by autopsy (Dejerine and Theoary, Casassus and Ramsay Hunt). The deduction from a study of these reports is that involvement of the peripheral branches is constant; the trunk is equally affected; the roots remain free, and the nuclei are the seat of important lesions.

Paralysis of the palate is often incomplete and always transient and benign. It occurs at the same time as the facial paralysis. Symptoms are few: slight deviation of the uvula to the sound side and sometimes lowering of the palatine arch. The duration is under two months. Only 4 cases of paralysis of the constrictors were found. Baldenwick and Decourt inclined to the view of a nuclear lesion; Federici and Hennebert thought that the lesion was truncular.

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ENCEPHALITIS IN ST. LOUIS. J. P. LEAKE, J. A. M. A. **101**:928 (Sept. 16) 1933.

Leake states that during the five weeks from August 7 to September 10, 1933, inclusive, there were reported in the city of St. Louis and St. Louis County 656 cases of encephalitis. It appears that the epidemic incidence for this area will not exceed a rate of about 1 case per thousand of population, and the reported extension of the infection to other places has thus far been remarkably slight. The case fatality rate will be about 20 per cent. Only 13 per cent of the cases have occurred among the 25 per cent of the population which is under 15 years of age, and 23 per cent of the patients have been in the age group from 15 to 34 years, which comprises 35 per cent of the total population. The recovery rate in these two age groups has been relatively high, with about half as many deaths in proportion to the number of cases as in the other two age groups. Of the cases 29 per cent have been among the 27 per cent of the population that is from 35 to 54 years old. The age group over 55, comprising only 13 per cent of the population, has had 35 per cent of the cases, and the case fatality in this oldest age group has been about double the rate for the other age groups. There appears to be no racial or sexual predilection save the usual preponderance of males in the age group under 15. Clinically, this outbreak has resembled other epidemics of encephalitis, but especially that described as occurring around the Inland Sea of Japan in 1924.

EDITOR'S ABSTRACT.

ENCEPHALITIS IN ST. LOUIS. EDITORIAL, J. A. M. A. **101**:932 (Sept. 16) 1933.

The article abstracted above is the basis of this editorial on the epidemic of encephalitis in St. Louis and St. Louis County, in which more than 115 deaths have occurred and the number of cases continues to increase, now totaling approximately 656. Occasionally cases of epidemic (lethargic) encephalitis appearing in other parts of the country tend to be confused with the situation that exists in Missouri. The

condition that has appeared in epidemic form in St. Louis County is not, apparently, the usual epidemic encephalitis but a new form classified as encephalitis B, and identified by health authorities with a similar condition which has previously occurred in Japan and Australia. The United States Public Health Service, the United States Army Medical Corps and both local and state officials have combined in an intensive study of the condition, without thus far having obtained more than a slight lead toward establishing its nature and with little, if any, knowledge of its means of transmission. Without definite knowledge of the cause of the disease or of its mode of transmission, it is impossible to establish any certain method of prevention or control. Moreover, as far as is known, there is nothing specific in the treatment for this disease. Such treatment as is now being given is supportive, including intravenous injection of dextrose and the usual symptomatic care.

All indications thus far determined as to the cause of the condition point to an unidentified virus capable of passing a Berkefeld filter and therefore susceptible of demonstration only by its ability to produce disease when injected into animals. Available reports indicate that monkeys have been inoculated, with the occurrence thereafter of fever and tremor and the weakness characteristic of human beings in whom this disorder develops. Both horses and mules have been inoculated with material taken from the brains of those who have died of the disease, and it is reported that a similar condition was produced in one of these animals. The scientists who are conducting this collective investigation may be depended on to continue their work with the vast material now available from those ill with the disease and from those who have died of it.

There has been some attempt to determine whether or not mosquitoes, which are present in St. Louis in unusual numbers, may not be associated with the transmission of the disorder, but thus far such experiments have not been at all conclusive.

In the meantime, physicians throughout the country should report at once to health officers in their localities the occurrence of any well established case of a similar disorder, or even any case that seems to be slightly suggestive of this disorder. Although the condition seems for the present to be rather well localized in St. Louis County, it is impossible to predict when cases may appear in some other community. If they do, the mere fact of that appearance may afford an invaluable clue to the mode of transmission. Physicians everywhere must be alert for the occurrence of this disorder. Certain symptoms should lead to suspicion of the diagnosis of encephalitis B: sudden onset, high temperature which lasts about a week and then declines, headache, occasionally diplopia, occasionally lethargy, but also tremors and convulsions. Lumbar puncture reveals clear spinal fluid usually under pressure, with a high cell count and with globulin and sugar, and the blood count shows a leukocytosis of from 15,000 to 20,000. It is conceivable, as with poliomyelitis and other conditions involving the nervous system, that there may be occasional cases so mild as to be overlooked. Patients thus affected, however, on becoming well, act as carriers of the disorder to other people. Epidemiologists are inclined to postulate special sensitivity or a natural immunity in some instances, which may be the reason for a single case occurring in many families. It is the history of similar disorders that the coming of cold weather is associated with their gradual disappearance.

EDITOR'S ABSTRACT.

DYSPITUITARISM: TWENTY YEARS LATER. HARVEY CUSHING, Arch. Int. Med. **51**:487 (April) 1933.

This paper is too lengthy and too well written to permit of adequate summation in abstract. Many aspects of pituitary physiology are mentioned, but for the most part the article is concerned with the symptomatology and pathology of adenomas of the gland. The hypophysis is composed of chromophobic cells which, when ripened, become chromophilic. The latter are of two sorts, acidophilic and basophilic. The mother cells, which outnumber the others, appear to have no secretory function. The basophils are apparently associated with sexual matura-

tion, while the acidophils elaborate a growth-promoting principle. Adenomas are classified according to the dominant cell, as chromophobic, acidophilic or basophilic. Tumors of the first type consist of nonstainable cytoplasm; they produce no recognizable constitutional disorder until they reach a size sufficient to expand the bony and membranous envelop of the hypophysis. Symptoms which are hypopituitary in nature are due to inactivation of the gland by its compression against the capsule; the syndrome is thus mechanical rather than secretory. This is the commonest of adenomas, two thirds of Cushing's series being classified in this group. An illustrative case is cited and reported in detail. The patient was a pituitary dwarf showing hypopituitary symptoms. A chromophobe adenoma was found and removed, an operation which resulted in disappearance of the headache and of the visual contractions. A second operation was necessary, resulting in similar beneficial effects. Some years later many of the symptoms returned, but this time a modified anterior lobe pituitary preparation was given intramuscularly. The daily dose was 2 cc. at first, increased to 3 cc. a month later, and to 4 cc. a month and half after the first increase. On this therapy, appetite increased and gain in weight was marked.

Two cases of excessive tallness are cited, with growth apparently checked by irradiation of the pituitary gland.

The acidophilic adenoma receives relatively little attention in the paper. Its association with gigantism and acromegaly is well known, and it appears certain that the growth hormone is actually a product of the secretory activity of the acidophilic elements. Reference is made to work showing the absence of these cells in the glands of hereditarily dwarfed mice. One question, however, is raised. Why should acromegalic states so often be accompanied by dystrophic changes in the reproductive apparatus? Apparently involvement of the neighboring basophilic elements is inescapable. Experimental evidence seems to show, however, that theoretically a pure growth hormone does exist.

The function of the basophilic cells is debatable. What evidence there is points to a sexual function. Fourteen cases of basophilic adenoma are culled from the literature and tabulated. Obesity occurred in thirteen of the fourteen; amenorrhea in all twelve of the cases in females, and impotence in both of the male patients. The twelve females displayed abnormal distribution of hair. In the seven cases in which an adequate urinalysis was made, glycosuria was present. In eight patients a metabolic study had been made; four showed an increase, and two a reduction in rate. Nine were studied for the status of bone and calcium; eight had skeletal decalcification or fracture. In all ten of the patients examined for this sign, atrophy of the gonads was found.

Whether the obesity so constantly present is a pure pituitary sign or represents involvement of the tuber is discussed. Cushing does not believe that the tuber is always injured by enlargement of the gland, for obesity often occurs in glands of normal size. He postulates a tuberohypophyseal mechanism hyperactivated by secretory products from the pars intermedia. The polyuria and polydipsia, often associated with the syndrome, are suggested as corroborative evidence of this hypothesis. The hypertension can be explained on the basis of excessive neurohypophyseal secretion without reference to involvement of the suprarenal glands. Suggestive of the correctness of this explanation is the fact that destructive lesions of the posterior lobe are associated with low blood pressure.

Secondary endocrine effects are discussed in some detail. Involvement of the thyroid, parathyroid and gonadal glands and the pancreas with reference to dyspituitarism are reviewed. From the wide diversity of information, experimentation, fact and fancy, it becomes evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body.

The paper, 70 pages long, is annotated by 140 references, and illustrated by 34 figures and diagrams.

DAVIDSON, Newark, N. J.

AN EVALUATION OF PSYCHOANALYSIS. EDITORIAL, J. A. M. A. **101**:1643 (Nov. 18) 1933.

The article of Leo Kessel and Harold Thomas Hyman (*J. A. M. A.* **101**:1612 [Nov. 18] 1933) on "The Value of Psychoanalysis as a Therapeutic Procedure" represents a rare—and in American medical literature—perhaps even a unique occurrence. It is an objective and an entirely unemotional report of therapeutic results in thirty-three patients treated by accredited psychoanalysts in New York. Its merit lies particularly in the fact that it lacks any preconceived tendency to discredit this new approach to psychogenic disturbances. The authors subject the psychoanalytic results to the unbiased critical scrutiny they would use in evaluating any other form of therapy. In 1930 the Berlin Psychoanalytic Institute published a careful statistical evaluation of 721 patients who had been treated in the period of ten years by its staff, all the members of which are psychoanalysts accredited by the International Psychoanalytic Association. This statistical report, however, was prepared by psychoanalysts. Perhaps a parallel to Kessel and Hyman's fair attempt at evaluation of the work of psychoanalysts is the report published four years ago by the commission of the British Medical Association. This commission was entrusted with the difficult task of evaluating psychoanalysis as a medical theory and procedure. Its report, however, though entirely objective in tone, was not based on statistical analysis of cases in which psychoanalysis was used.

The attempt of Kessel and Hyman to arrive at objective conclusions regarding the therapeutic value of psychoanalysis is in itself so significant that possible disagreements regarding smaller details of their statistical analysis seem unimportant. Final conclusions can hardly be drawn from a study of such a small number of cases. This is especially true because their study includes cases of such diverse nature as schizophrenia and mild behavior problems. The majority of psychoanalysts at present seem to consider the concepts of psychoanalysis most helpful for understanding the meaning and structure of schizophrenia but feel at the same time an adequate therapeutic technic for such cases has not yet been developed. The application of psychoanalysis to schizophrenia is still definitely in an experimental stage.

Naturally, many psychoanalysts will question the soundness of some of the principles followed by the authors in the evaluation of therapeutic results. Kessel and Hyman consider it an evidence of failure of the analysis if the analysis ends with a change in the life situation (marital status) of the patient which is contrary to the purpose with which the patient started his analysis, even though the symptoms and the neurosis may have been cured as a result of the treatment. The objection of psychoanalysts would be that frequently the patient's life situation, as, for example, his marriage, has been itself the result of his neurosis. Neurotics, it is said, often choose unsuitable marital partners just as they choose unsuitable vocations, as a result of certain neurotic trends. In such cases it is quite unavoidable that the patient's cure sometimes results in his reorienting himself in his life situation. Leading psychoanalysts claim that improvement of a marital relation is a more frequent outcome of analysis than is divorce. In any case the neurotic patient's expectations and demands at the beginning of the cure are frequently integral parts of his neurosis. It is at present a recognized principle in psychoanalytic practice, as in therapeutic science generally, that, in accepting a patient for treatment, the analyst or physician should not allow the patient to prescribe the conditions for his cure. Just as an internist could not possibly allow a diabetic patient to demand that he be made capable of tolerating a diet of the patient's own choice, so also is it not permissible for a psychoanalyst to undertake the task of making a violin virtuoso out of a person without musical talent.

There is no question that both psychoanalysts and other physicians will welcome statistical studies, such as Kessel and Hyman's, which alone can form the basis for sound conclusions regarding the therapeutic efficiency of psychoanalysis. Psychoanalysts, however, will probably feel that the significance of psychoanalysis lies not only in its therapeutic value but perhaps even more in its method of

scientific approach and in the theoretical concepts which it contributes to the better understanding of psychopathologic phenomena. They maintain that the soundness of their concepts and methods of studying mental phenomena should warrant the hope of further improvements in therapeutic technic.

NUTRITION IN RELATION TO ANAEMIA. L. S. P. DAVIDSON, H. W. FULLERTON, JAMES W. HOWIE, JOHN M. CROLL, J. B. ORR and W. GODDEN, Brit. M. J. **1**:685 (April 22) 1933.

Recent advances in hematology indicate that nutrition may play an important part in the production of anemia. Other investigators have shown that when an experimental animal was fed milk alone a hypochromic anemia developed, and the rate of growth of the animal was seriously reduced. Others have shown also that the prolonged feeding of cow's milk to infants produces anemia, a condition which can be cured or prevented by the addition to the diet of a few grains of iron and ammonium citrate daily. These anemias may be classified as direct deficiency diseases. The investigation reported in this paper was undertaken to ascertain whether anemia was prevalent among the poor, and if so, whether its origin lay primarily in dietary deficiency or whether it was influenced by such factors as menstruation, pregnancy and infection, and finally whether this anemia responded successfully to iron therapy.

The majority of the cases investigated occurred in families in which the wage earner was unemployed. The great majority were apparently healthy persons who had presented themselves at the institution not for medical attention, but as escorts to their children or friends, for whom advice was sought. Five hundred persons were examined, of whom 455 were women and 45 men. In addition, 100 children from families in the same class of the community were examined, the children being taken equally from families in which the mothers were anemic and non-anemic. Lastly, 650 children were investigated by Dr. Sutherland, of Peterhead, with reference to vitamin A as a prophylactic agent in regard to infection. No blood tests were performed in this group, but the children were carefully examined clinically on two occasions for evidence of anemia.

Of the 45 adult males, only 5 were found to be anemic. Three had hemoglobin levels between 70 and 85 per cent, while in 2 the levels were below 70. In 3 of these cases the patient suffered from a physical condition which might account in part for the anemia. Of the 455 adult females, 46.8 per cent had hemoglobin values below 85 per cent, and of these 13.8 per cent were below 70. Only 2 of the 100 children from poor families were found to have a hemoglobin percentage below 85, and of the 650 children in Peterhead only 6 were found to be anemic in the first examination, and only 8 in the second. Thus, anemia is relatively uncommon in children between the ages of 5 and 14 years and in the adult male, but is very prevalent among women of child-bearing age of the poorest classes, since it was found to be present in nearly half of the patients examined.

Investigation was then made to determine the correlation between the iron content of the diet and the incidence of anemia. The average diet of the families with cases of anemia was found to be very similar to that of families without cases of anemia. In fact, the families with anemia were taking a slightly better diet than the families without anemia, and there did not seem to be any correlation of the diet and the hemoglobin content of the blood. Similarly, the intake of copper seemed to be about the same in the two groups. It was found that menorrhagia and pregnancy or recent childbirth are the factors which appear to bear the most direct relation to the degree of anemia. In the authors' opinion, the rôle of "infection" in the production of anemia is of only subsidiary importance. Test meals were given to 28 persons who had the more severe types of anemia. More than 89 per cent of the women in the group with anemia on whom gastric analysis was performed had achlorhydria or hypochlorhydria, as compared with 11 per cent of the women without anemia.

Twenty patients with the more severe anemia were treated by means of 30 grains (1.95 Gm.) of iron and ammonium citrate three times a day. The increase in hemoglobin percentage in the red blood cells was remarkable. It is suggested, on the basis of these findings, that a glass of milk and a pennyworth of iron and ammonium citrate, without additional change in the diet of pregnant women of the poorest classes, would produce remarkably beneficial results to mothers and infants.

FERGUSON, Niagara Falls, N. Y.

THE MOTHER: AGENT OR OBJECT? IAN D. SUTTIE and JANE I. SUTTIE, Brit. J. M. Psychol. **12**:91 and 199, 1932.

The authors advance a concept of parent-child relationships which is unusually interesting, and which is well worth careful reading. The mother-child relationship is discussed in considerable detail. The infant, according to the writers, after the stage in which he knows only the self, receives the greatest trauma of his life when he learns that his mother is an independent being, differentiated from the self. He does not then identify with her, in the freudian sense of identification, an introjection of the loved object; in his psychologic development he must achieve separation from her. The mother, and this commonly occurs in a patriarchal form of society in which she is thrown back on the child because she is deprived of other interests, can fix the child's interest in herself, until it acquires a personal and sexual interest. The authors believe that Freud overemphasizes the sexual strivings of the pre-Oedipus stage, although in a recent article (Freud, S.: Female Sexuality, *Internat. J. Psycho-Analysis,* pt. 3, 1932) he has in part (i. e., for the girl but not for the boy) corrected this error. The authors believe that the pre-Oedipus attachment of the child, boy or girl, rests on an associative basis, a clinging to the mother. The nutritive element is also important here.

The father's relation to the child assumes an important rôle in a patriarchal culture, because he is the bread-winner; thus he competes with the mother for participation in this phase of the child's life, feeding. For the father may represent not merely a feared object because of repressed hostility on the part of the child, to whom he represents the hated rival for the mother's love. The father is actually hostile to the child because of a jealousy situation analogous to sibling rivalry, and having its roots in the father's biologically unimportant rôle, since the mother suckles the child.

The mother, however, rather than the father, frequently acts as the repressing agent of the child's Oedipus wishes. Maternal repression, if on the right lines, is so effective that no recognizable Oedipus symptoms erupt—the child realizing that in the Oedipus fantasy "mother is not willing," and fearing the loss of her love rather than the punishment of the father. Maternal repression makes for health; paternal repression for neurosis or sublimation of various sorts. Only when there is inadequacy in maternal repression does there appear the father-son antagonism and the Oedipus complex.

The Sutties would discard the present psychoanalytic concept of the death instinct as biologically unsound; aggression is not part of a destructive instinct, but a response to frustration. The desire for death is not innate in man, but again a clinging to the mother, a desire for union with her. They outline how this mechanism may operate in schizophrenia and melancholia. The self-preservative instinct, an important component of which is hunger, becomes differentiated in the infant from an original formless, plastic, associative craving. Sublimation is entered on later as a deflection of love from the mother, as a cooperative interest in her activities, and in a desire to please her. This is an important consideration in education.

No critical analysis of the material in terms of various systems of psychology and psychoanalysis is attempted by the reviewer. The article is well written, draws analogies from anthropology, biology and religion, and contains a wealth of

material which has many interesting as well as practical aspects that make for a clearer understanding of the mother-child relationship. It will be read with interest.

ALPERN, Philadelphia.

A COMPARATIVE PHARMACOLOGIC STUDY OF ABSORPTION, DISTRIBUTION, AND EXCRETION OF INJECTABLE BISMUTH PREPARATIONS. MARVIN THOMPSON, G. E. CWALINA, C. T. ICHNIOWSKI and BERTRAN S. ROBERTS, Am. J. Syph. **17**:205 (April) 1933.

The efficacy of bismuth preparations in treatment for syphilis depends on the absorption of significant amounts of bismuth, and the consequent appearance of effective quantities of the metal or its salts in the tissues. The purpose of the study here reported was to determine differences, if any, among five typical preparations as to absorption, toxicity, irritation and excretion. The compounds used, indicated by number, were (1) alpha carboxethyl betamethyl nonate of bismuth, 40 mg. of metal per cubic centimeter in oil; (2) bismuth sodium tartrate in aqueous solution, 11 mg. of metal per cubic centimeter, with dextrose as protective colloid; (3) aqueous preparation of colloidal bismuth hydroxide, 4 mg. of metal per cubic centimeter; (4) water-soluble bismuth thioglycollate, 37.5 mg. of bismuth per cubic centimeter; (5) bismuth sodium gluconate, corresponding to 12.5 mg. of bismuth per cubic centimeter in colloidal solution (aqueous).

The preparation was injected into the center of the heaviest part of the gluteal muscle of a dog. The dose was in terms of metallic bismuth, graded according to the weight of the animal. To determine rate of absorption, the experimenters measured the bismuth remaining in the gluteal muscle at various intervals from the time of injection. The amount of the metal in the significant organs was also assayed. Observations were made daily on the behavior and appetite of the animal to determine clinical toxicity. Urinary determinations were made to gage the amount of excretion.

Of the five preparations, no. 4 was absorbed most rapidly; then in order, nos. 3, 2, 5 and 1. Tissue distribution and urinary excretion followed the same order, bismuth appearing in the tissues soonest in animals which had received no. 4, and urinary output being greatest in the same animals. The most irritating of the preparations were nos. 2 and 5; these produced hardening, discoloration, edema, coagulation of muscle fibers and even necrosis. Numbers 1 and 4 produced no obvious irritative effects, and no. 3 very little.

None of the dogs receiving therapeutic doses gave any evidence of pain or toxicity. In very large doses, however, no. 4 was poisonous, and for some dogs even fatal. Next in order of toxicity was no. 3, with nos. 1, 2 and 5 following in that order.

The authors warn against concluding that rapid absorbability is the essential factor in therapeutic effectiveness. They point out that excess amounts may be stored and rendered ineffective, or may be excreted rapidly with injury to the kidneys or liver. It is possible that the more slowly absorbed preparations may prove as effective as the others, with less toxicity and more prolonged effect.

DAVIDSON, Newark, N. J.

CROSSED OCULAR REACTIONS. A. MAGITOT, Ann. d'ocul. **170**:501 (June) 1933.

Experiments have shown that certain physiologic reactions are produced in one eye by the excitation of the other eye. These oculo-ocular reactions, discussed in studies of sympathetic ophthalmitis, are exaggerated manifestations of normal phenomena and are similar to the reflex of Brown-Séquard and Tolozan affecting the extremities. The crossed oculo-ocular reactions consist mainly of ophthalmotonic, vascular and corneal variations and of chemical modifications of the aqueous humor. Ocular compression, simple contusion, cauterization of the limbus, crushing of the ciliary ganglion, subconjunctival or intra-orbital injections of

irritating substances and injections of various fluids, even a few drops of isotonic serum, into the vitreous are likely to produce these oculo-ocular reactions. The simple projection of light on the anterior segment of one eye is sufficient to modify the biomicroscopic appearance of the vessels of the iris of the opposite side.

Many clinical observations have confirmed the evidence of these experiments. Modifications of tension after contusion or accidental injections into the vitreous are followed by the same contralateral reactions as have been shown in the experiments on animals. These crossed reactions are more frequent and more marked in glaucomatous than in other patients. The crises of hypertension which occur in the normal eye when the diseased eye is operated on are in reality a transfer of excitation. In bilateral glaucoma, a decompressive operation on the eye most affected may cause the disappearance of all glaucomatous symptoms in the other eye. Also, the enucleation of an atrophic and painful eye may have the same decisive and favorable influence on the evolution of a contralateral glaucoma.

In this category, certain cases are found in which compression of a hypotonic and painless eye causes an intense hypertension in the other eye. All these manifestations, as well as the experiments in the dark and in the light, are vasomotor oculo-ocular reactions. In fact, each eye has an intraparietal organovegetative center, probably formed by the choroidal ganglion of Müller. These intraparietal centers, which are important in the circulation of the blood of the eye, are bound by nervous connections to the peripheral centers (ciliary ganglion and superior cervical ganglion). These right and left peripheral centers are also united by association tracts, because excitation of the oculovasomotor nerves at the base of the neck causes a bilateral modification of the chemistry of the aqueous humor. External orbitotomy produces the same effects.

The vasomotor oculo-ocular reactions may be considered as the result of stimuli started on one side by the action of the intraparietal center and from there transferred to the homolateral peripheral centers, from which the crossed association tracts carry them to the centers of the opposite side, and then to the fellow eye.

BERENS, New York.

EXPERIMENTAL TOXIC APPROACH TO MENTAL DISEASE. A. FERRARO and J. KILMAN, Psychiatric Quart. **6**:582 (Oct.) 1932; **7**:115 (Jan.) 1933.

Reviewing the evidence of the importance of toxic factors in mental disease, Ferraro and Kilman propose to study the reaction of brain tissue to the injection into the body of indol and histamine. Indol, formed in the large bowel, is a by-product of intestinal putrefaction; its formation in excess is commonly associated with indicanuria. The amount of indol normally present in 100 Gm. of fresh stool varies from 5 to 20 mg., but amounts of 50 Gm. or more may be obtained in toxemias and other pathologic states. Histamine originates from decarboxylization of histidine, whether this process be bacterial or fermentative. The normal yield per 100 Gm. of feces varies from 1 to 4 mg.

The authors injected indol or histamine, or both together, into cats and observed the results clinically and pathologically. The protocols of nineteen cases are reported in such detail as to make abstracting of the findings impossible. Unfortunately, the authors failed to present any tabulation or summary of results. From a reading of the protocols, however, certain conclusions may be drawn. Both of the toxins caused serious damage to the central nervous system, and when injected simultaneously the effects were proportionately greater. Clinically, indol tended to make the animals restless, histamine to make them quiet or even stuporous; the latter drug often resulted in specific neurologic findings, such as muscular weakness, mydriasis, twitchings and tachycardia. The neuropathologic changes varied with the amounts injected. Chromatolysis of cortical cells was usually observed, degeneration being more pronounced in the frontal areas. Roundish metachromatic substances were noted in the white matter—a change occasionally found in normal brains. Astrocytes exhibited swelling and granular changes in the cytoplasm, with tortuosity of the processes. Clasmatodendrosis was

marked, especially in the diencephalon. In the cerebellum the Purkinje cells underwent homogenization, with the elements gradually disintegrating.

The experiments point to changes in the central nervous system following the use of enterogenous toxic substances, leading to a contention on the part of the authors that the nervous symptoms which the injection of these toxins produces in man are related to the pathologic changes which these toxins appear to cause. This is further supported by the favorable influence on mental symptoms which has sometimes been reported following gastro-intestinal therapy. Instances of this favorable influence, however, are not specifically cited. Ferraro and Kilman believe that by paying more attention to toxic agents in the psychoses it may be possible better to evaluate the therapeutic measures likely to relieve sufferers from mental disease.

DAVIDSON, Newark, N. J.

HISTOPATHOLOGIC STUDIES OF ENCEPHALITIS AFTER CHICKENPOX (ENCEPHALITIS POSTVARICELLOSA). L. VAN BOGAERT, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:201 (June) 1932.

During the course of a severe case of chickenpox in a girl aged 12 there developed an intense meningeal reaction, followed later by an acute ataxia with choreiform movements, pyramidal disturbances and insomnia. There were a bilateral Babinski sign and incontinence. Lumbar puncture revealed an increased pressure, with hyperalbuminosis but no increase in the cell count.

Study of the brain revealed an acute degenerative involvement situated chiefly in the cerebrum and cerebellum, but also in the basal ganglia. There was a diffuse infiltration of the gray masses, in foci at the junction of the gray and white matter and in the white matter of the cerebellum. The areas of demyelinization varied in size from that of a miliary focus to that of a cerebellar leaflet. Often they were situated around vessels, but not as much as in measles and postvaccinal encephalitis. The pallidum was particularly involved, the thalamus less, and the caudate and putamen almost not at all. The frontal and parietal areas were the chief fields affected in the cortex. The Betz and Purkinje cells were particularly involved. The substantia nigra, the gray formations in the pons and medulla and the olivary bodies were intact. The spinal cord showed a slight infiltration around the posterior and anterior roots. The peripheral nerves (sciatic, popliteal, radial and ulnar) were intact. So, too, were the spinal ganglia, the cervical sympathetic and solar plexus ganglia and the gasserian ganglion. Meissner's and Auerbach's plexuses were not examined.

The areas of demyelinization were present chiefly in the centrum ovale (frontal, parietal and temporal), in the cerebellum and in the inferior cerebellar peduncle. They were not found elsewhere; the cord in particular was not involved. The ganglion cells in the cortex were not much involved, except for those mentioned. The axis-cylinders were rather markedly involved, even outside the foci of demyelinization. Gliosis, especially by fibrous glia, was marked in the foci.

The picture seems to resemble closely that of multiple sclerosis. It differs from it in the fact that, in contrast, the axis-cylinders are also involved. This has been demonstrated before by others. In addition, the absence of foci in the gray masses is not in keeping with multiple sclerosis. The localization of the lesions in encephalitis following chickenpox is of great significance and is similar to that after vaccination and measles. A similar case reported by Zimmermann and Yannet differs from that of van Bogaert in the absence of perivascular plaques and of inflammation, as well as in the acuity of the lesion.

ALPERS, Philadelphia.

A CASE OF MULTIPLE SCLEROSIS WITH MAINLY MENTAL SYMPTOMS. C. I. URECHIA and N. ELEKES, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:370, 1933.

Psychotic symptoms occur more or less frequently as additional manifestations of multiple sclerosis. Varying from mild disturbances of character to severe psychotic manifestations, and including manic outbreaks (Lewis), paranoid or

dementia paralytica-like attacks (Raecke), simple dementia and hysteria, they form an assortment of pictures which may offer great difficulties in diagnosis. The psychotic manifestations are only the clinical expressions of the fact that patches will be found in the cortex. At times the cortex is the main location of the patches. It is true that cases occur frequently in which, in spite of numerous cortical plaques, the psyche is completely intact; on the other hand, cases are described in which there are psychotic symptoms without cortical plaques. If the mental symptoms occur after manifestations of involvement of the spinal cord, it is probable that the mental symptoms are due to cortical lesions. Usually the mental symptoms are only a part of the clinical syndrome, but occasionally they occur without neurologic manifestations of the underlying pathologic process. It is in cases of this sort that diagnosis is difficult, if not impossible. It is about this type of case that the present article is written.

The case presented is that of a woman, aged 28, whose illness began in 1917 with cerebral symptoms of a stormy meningo-encephalitic nature, with high fever, confusion and delirium. After the acute symptoms subsided there remained a severe defect of intelligence, with confabulation of the Korsakoff type. Bodily symptoms were completely absent, and there was nothing on which a diagnosis of multiple sclerosis could be made. For fourteen years the condition remained stationary; autopsy gave the first clue as to the correct diagnosis. At times psychic symptoms have been present as early symptoms of multiple sclerosis, but only rarely have they been the sole symptoms. The pathologic anatomy also showed peculiarities. Aside from the numerous cortical plaques which showed no inflammatory or proliferative manifestations, as is usual, there were also a deep and a diffuse degeneration of the parenchyma, which involved particularly the superficial layers. The subcortical foci were characterized by a tendency to status spongiosus, with the formation of large cysts in places. Why so many foci in the subcortex, basal ganglia, pons and cerebellum produced no bodily signs remains a mystery, as do many other problems of this disease.

WINKELMAN, Philadelphia.

DEGENERATION OF GANGLION CELL FOLLOWING AXONAL INJURY. GEORGE R. JAMES, Arch. Ophth. **9**:338 (March) 1933.

Degeneration of the ganglion cell invariably follows serious injury to the axon. In order to determine the progress and end-results of such degeneration, an experimental study was carried out. Considerable work has been done on this subject in the past. Degenerative changes were studied and first described by Nissl in 1892. In his description the statement first appeared in the literature that the Nissl bodies showed progressive disintegration of the chromatin material in the cytoplasm. Bielschowsky, Marinesco, van Gehuchten, Birch-Hirschfeld and others attempted to determine, if possible, the end-results of chromatolysis in the ganglion cells.

In this study, the optic nerve was severed, and the rabbits were then killed by a blow to the back of the neck after one, two, five, ten, twenty, thirty, sixty and one hundred and twenty days. In each instance the opposite eye was retained as a control for both gross and microscopic comparisons. The ganglion cells of the retina in these rabbits showed the same reaction to axonal injury as do other nerve cells of the central nervous system. In the early stages the cells stained poorly, and chromatolysis appeared in the central areas; i. e., the Nissl bodies stained less densely and had a granular appearance. Later, the protoplasm of the cell apparently became swollen, the Nissl material disappeared, and the cell faded away. The nucleus was the last to change, there being no swelling but only a gradual disappearance.

Ten days after the injury to the axon, practically all ganglion cells in the retina showed chromatolysis. By the twentieth day most of the cells were so much degenerated that only the nucleus and fragments of the cell body remained. Between thirty and sixty days large ganglion cells of normal appearance were rare. At

sixty days some of these cells showed chromatolysis. At one hundred and twenty days an occasional cell, apparently of the small ganglion cell type, was found.

It appears that the period of greatest degeneration and dissolution in the ganglion cells occurs between the tenth and twentieth day after section of the axon. After from thirty to sixty days, there is evidently some effort at regeneration, but such an effort is apparently unsuccessful since chromatolysis eventually appears in these few cells. Whether the rare ganglion cells found as late as one hundred and twenty days after injury to the axon are cells that are recovering from injury or cells that sent no axons into the optic nerve is a point that is at present undetermined.

SPAETH, Philadelphia.

AMNESIA IN RELATION TO CRIME. J. S. HOPWOOD and H. K. SNELL, J. Ment. Sc. **79**:27, 1933.

The authors studied 100 patients, in the state criminal asylum at Broadmoor, who claimed amnesia in connection with the crimes which they had committed. The family histories showed frequent incidents of mental disease in antecedents and siblings. In the personal histories of the patients alcoholism was found in 97 per cent, epilepsy in 19 per cent and a previous attack of mental disorder in 14 per cent of the cases. Only 3 patients were total abstainers. The majority of crimes were attempted or committed murders, and in one half of the cases the crime was done in connection with a sweetheart or a very close relative. Some of the other important conclusions are: "Amnesia cannot be diagnosed on the patient's word alone. His story must be checked by known facts, independent evidence being absolutely essential before an opinion can be formed. The first account given by the patient is of paramount importance and should be recorded with all the detail he can provide. Subsequent variations in his story are to be regarded with skepticism. While real recovery of memory does not occur until some weeks or months after the crime, allowance must be made for some slight alteration in the memory defect from day to day in a few cases where the loss of memory is only partial. A patient who remembers points in his favour and conveniently forgets everything else is probably malingering. A history of chronic alcoholism or of other indications of a psychopathic personality, including a previous loss of memory, is frequently elicited. The existence of a neuropathic heredity is to be expected in a fair number of cases. The character of the alleged amnesic period is of foremost value. In genuine cases the beginning and more especially the end are frequently blurred, and usually the loss of memory prior to the committal of the crime is of much shorter duration than that of the subsequent period before normal consciousness resumes control. Where the amnesia is partial and the patient has a confused recollection of his acts, the ideas accompanied by marked emotion are remembered, while those with less emotional tone are not. Statements made soon after the crime showing a knowledge of the act are not incompatible with genuine amnesia due to a later repression. The crime is frequently without motive, and is carried out in a way which shows that the individual was not acting with premeditation, and he makes no attempt to escape from the consequence of his actions. A sudden return of memory almost certainly indicates malingering."

KASANIN, Howard, R. I.

DEVELOPMENTAL CRANIO-CEREBRAL TOPOGRAPHY. WILLIAM T. PEYTON, J. Nerv. & Ment. Dis. **78**:232 (Sept.) 1933.

The topographic relations of the fissures, sulci and convolutions to the wall of the cranial cavity are variable, depending on a large number of conditions. The three main factors are age, sex and the shape of the skull. Peyton gives a résumé of the various methods used in the effort to investigate this cerebral topography. De la Foulhouze and Dana studied the relation of the fissure of Rolando in a series of persons and found that it was more nearly parallel to the coronal suture. Féré concluded that the sulcus centralis is posterior to the

coronal suture in all cases, from the time of its appearance in the fetal brain. It gradually becomes more vertical until birth, but after birth the obliquity again increases gradually and in the adult it is nearly as great as in the fetus. The lateral fissure is widely open throughout its extent in the fetus and partially closed in the new-born. The sylvian point is located accurately by the pterion.

Peyton employed what is called the orthoscopic method in a study of ten brains from one fetus, five new-born infants, two children and two adult males. Intra-arterial injection in the adult specimens and injections of formaldehyde in the others were performed. The method of obtaining silhouettes of brain areas was that described by Scammon. He concludes that the silhouette area of the cerebrum expands rapidly during the last month of fetal life and the first eight months of postnatal life, but that after the fifth year there is very little change.

The superior rolandic coronal distance was found to increase with age, but the distance and the increase with age were not as great as had been reported by other investigators. The inferior rolandic coronal distance was found to increase more than the superior, and the distances at various ages were practically the same as those given by other workers. The superior end of the central sulcus was found to approach the squamous suture between birth and maturity. The lateral fissure was found also to approach the squamous suture between birth and maturity. These distances were approximately the same as those given by other observers for the various ages. The silhouette area of the lateral ventricle increased very little during the period of growth studied. Its posterior and lateral horns appeared to extend farther posterior during the period of growth studied, but the anterior horn appeared to remain approximately stationary in the horizontal plane during the same period. HART, Greenwich, Conn.

HEMISUDATION OF THE FACE IN PAROXYSMS EXCITED BY COLD AND APPEARING AFTER AN ENDONASAL OPERATION. H. ROGER, Y. POURSINES and J. ALLIEZ, Rev. d'oto-neuro-opht. **11**:508 (July-Aug.) 1933.

The interest in the case reported lies in the fact that the cause of the condition was an endonasal operation. In one of Worms' cases the hemisudation followed traumatism of the external nose, and in a case reported by André-Thomas and Bars it followed, after two years, the removal of nasal polyps and resection of the inferior turbinates.

A month after resection of both middle turbinates, which was accompanied by hemorrhage and tamponade of the left nostril for a week, the patient began to sweat on the left side of the face. The sweating was located on the forehead, the malar region and the temple, occasionally extending to the occipital region. While mastication brought on the paroxysm, exposure to cold was the most active excitant. The sweating was more intense in winter and varied with the weather; it disappeared when the patient was warm in bed. A general examination, the Bordet-Wassermann test and ocular examination gave negative results. There was more congestion in the left side of the face, and razor cuts there bled more freely. The left middle meatus of the nose was blocked by a deviation of the septum. Irritation of the mucosa of the left nostril caused more lacrimation than that of the right, and discrete sweating of the nasal ala and forehead. A subcutaneous injection of pilocarpine hydrochloride caused more sweating of the left side of the face than elsewhere. An injection of 0.25 mg. of atropine did not diminish the suboral hydrorrhea. In spite of this result, a daily dose of 1 mg. of atropine controlled the sweating for four or five hours.

Other abnormal sympathetic reactions are known. Hallion and Comte observed a patient with advanced trophic and anesthetic trouble of the hand, in whom refrigeration produced vasodilatation. André-Thomas studied two cases of lesion of the "ganglion étoilé" in which there was no vasoconstrictor reaction to cold—the temperature was even elevated. In the case reported, the nasal mucosa was the seat of the sympathetic irritation. The effect of cold on the nasal mucosa is

to cause congestion and secretion, which irritated the sympathetic nerve wounded by operation, and the latter responded by a sudoral reflex.

DENNIS, Colorado Springs, Colo.

CHRONAXIMETRIC INVESTIGATIONS IN HEREDITARY AND FAMILIAL DISEASES OF THE NERVOUS SYSTEM. A. KRIENDLER and M. SCHACHTER, Arch. f. Psychiat. **99**:683 (April) 1933.

Studies of chronaxia were undertaken in the families of three patients suffering with familial forms of nervous diseases. The first of the patients was a boy with hereditary atrophy of the pectoral muscles. This condition was present also in the father. In addition, the patient had atrophy of the muscles of the little fingers of both hands, with contractions. This was not present in the father but was found in the patient's sister, and the history showed that a similar condition, without involvement of the pectoral muscles, was present in the patient's grandmother. The chronaxia of the muscles of the shoulder girdle, forearm and hand was studied in the father and sister and in the patient himself. The muscles that were actually affected presented either prolonged chronaxia or no reactions to the electrical stimulus. Muscles that did not show any clinical signs of the condition (e. g., the pectoral muscles in the patient's sister) showed much prolonged chronaxia.

The second patient had a familial facial paralysis, which was present in five siblings and in the father. Three other siblings showed no clinical signs of facial paralysis. The muscle groups the chronaxia of which was examined included all those supplied by the facial nerve. In addition, the chronaxia of the vestibular nerve was examined. Here, too, chronaxic disturbances could be elicited not only in muscles in which paralyses or weaknesses were present, but even in the cases of members of the family who had not as yet presented such disturbances.

The family of the third patient presented spastic familial paraplegia. Two sisters were examined. Although the clinical distribution of the paralyses differed in the two, the chronaxic disturbances found were in the same groups of muscles. Kriendler and Schachter conclude that: (1) members of families in which familial or hereditary diseases of the nervous system occur can be shown to have predispositions to these diseases even if they do not show clinical symptoms or signs; (2) families in which different members present familial neurologic disturbances affecting different groups of muscles show chronaxic disturbances in all the muscles that are affected in the different members. MALAMUD, Iowa City.

THE HYPOTHALAMUS OF THE ALBINO RAT. WENDELL J. S. KRIEG, J. Comp. Neurol. **55**:19 (June) 1932.

The hypothalamus of the albino rat was studied by a variety of technical methods, with special attention to fiber connections and cell types. Thirty-five series of sections were used. The Nissl, Cajal and Golgi technics were employed. The serial sections from a number of brains were divided into three groups; *A* was stained in toluidine blue to show cell structure, *B* was stained with alcoholic silver nitrate solution (Davenport) for nerve fibers, and *C* with iron hematoxylin (Morgan) for myelin sheaths. Atlases of the nuclear pattern of the hypothalamus were made in each of the three planes, from every third or every sixth section, and the nuclei differentially colored. Fibers were then added from the parallel Davenport and Morgan series, with further points from the Cajal series. Seventeen nuclei, some of which are subdivided, are described, and a schematic reconstruction is made embodying their space relations. Twenty different cell types of these nuclei are characterized and depicted.

A number of fiber groups passing to the hypothalamus are described and their intrinsic connections outlined. Their origins are derived chiefly from: the amygdala, tubercular and parolfactory areas, septum, preoptic region, hippocampus, lenticular nucleus and zona incerta. Thus the predominant afferent connection of

this region is olfactory, but connection is also made with centers the function of which is chiefly motor correlative. The efferent connections are limited to the dorsal longitudinal fasciculus (Schütz), the tractus filiformis lateralis and the medial forebrain bundle.

Krieg sees little evidence that this region controls vital functions and suggests that in higher mammals the vegetative functions, progressively becoming more elaborate, take over the relatively undifferentiated field of the hypothalamus, the olfactory importance of which is diminishing, and develop from it a center of vital processes. On the basis of structure he thinks that the following nuclei are vegetative: filiformis, supra-opticus, premamillaris lateralis and hypothalamicus lateralis.

A thorough survey of the literature on the hypothalamus from 1881 to the present has been included.

FRASER, Philadelphia.

THE SUPPORTING REACTION (STUTZREAKTION) IN MAN IN PHYSIOLOGIC AND PATHOLOGIC CONDITIONS. O. BALDUZZI, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:1 (Aug.) 1932.

Balduzzi correlates some of the findings of Rademaker with clinical states. He tested his cases by means of the Magnet reaction—pressure on the sole of the foot with subsequent tonus changes in the leg. He found that new-born infants have a series of reflex reactions similar to the supporting reactions of decerebellate animals. They are dependent on exteroceptive and proprioceptive stimuli, which come from the skin of the sole of the foot (particularly in the zone between the middle of the foot and the phalanges), from the deep tissues of the sole or from the mechanically stretched muscles through extension of the phalanges. These reactions begin at birth; it is possible that they may be obtained in premature infants of 7 months, as Balduzzi observed in two instances. They become more pronounced up to 6 months, and from this time on, as the infant becomes more capable of standing, they become less clear. These reflexes are definitely influenced by tonic neck and labyrinthine reflexes, which either inhibit or amplify them. Supporting tonus influences the tone of the opposite leg, which attempts to assume an extensor tonus.

Supporting reactions occur only under pathologic conditions in adults. Schwab found them in: (1) diseases of the frontal lobes (tumors, abscesses and cysts); (2) diseases of the temporal lobe; (3) involvement of the internal capsule; (4) cases with pontile, medullary and cerebellar symptoms. They occur usually on the side of the lesion. Forster considered these reactions as indicative of a lesion of the frontal or the temporal lobe of the same side. On the other hand, Pette found supporting reactions very rarely in cases of cerebellar disease. Markow, however, found them in four cases of cerebellar disease, in three cases of involvement of the frontal lobe, and in one case of temporoparietal tumor.

Balduzzi found that the supporting reactions occur with greatest frequency after injury of the cerebellum, less often after involvement of the frontal lobe, and still less in disease of the temporal lobe. They are always most marked on the side of the involvement.

ALPERS, Philadelphia.

TUBEROSE SCLEROSIS AND ALLIED CONDITIONS. MACDONALD CRITCHLEY and C. J. C. CARL, Brain **55**:311 (Sept.) 1932.

Bourneville, in 1880, was perhaps the first to recognize tuberous sclerosis as a pathologic entity. Marks of psychopathy were found in the family history in thirteen cases. Symptomatically, in true epiloia the first abnormality is usually delay in development, the mental defect usually being obvious by the third year. Within the first decade cutaneous lesions appear. After puberty the general course is rapidly down hill. The clinical course in the incomplete variant, formes frustes, may differ considerably. Most of the patients are undersized for their age, and stigmas of degeneracy are usually observed in the low grade patients. The chief neurologic findings have been flat tumors or "phakomas" on the retinas,

hypotonus in younger persons, which is replaced by rigidity in older patients, motor restlessness and occasional local paralysis. Critchley and Carl found cerebellar signs in only one case. Psychologically, there is a combination of intellectual defect proper with a primitive form of psychosis (always catatonic schizophrenia). In the high grade patients, the psychosis manifests itself at or after the fifth year; in the low grade, deterioration begins earlier. The most important dermatologic lesion of the skin is the facial adenoma sebaceum.

Pathologically, whitish, slightly prominent areas are found, usually only in the cerebral hemispheres. A marked anarchy in the stratification of the nerve cells, with regressive changes in the neurons themselves, and overgrowth of glia cells and foreign large cells characterize the microscopic appearance.

Four clinical variants are proposed: (1) adenoma sebaceum alone; (2) adenoma sebaceum with epilepsy, but with no mental change; (3) adenoma sebaceum with symptoms of cerebral tumor and (4) visceral tumor alone (including retinal tumors). Tuberous sclerosis may be regarded as (1) a hyperplastic disorder of the neuroglia originating during embryonic life or as (2) a widespread metaplasia affecting mainly the ectodermal tissues. It is thought that the similarities between tuberous sclerosis and Recklinghausen's disease have perhaps been overemphasized.

MICHAELS, Boston.

SOMATIC MOTOR MECHANISMS IN THE MIDBRAIN AND MEDULLA OBLONGATA OF CHRYSEMYS ELEGANS (WIED). HIDEOMI TUGE, J. Comp. Neurol. **55**:185 (June) 1932.

This is a topographic report of the motor system in the brain of the turtle preliminary to interpreting the development of behavior. Young animals were obtained from the market. Adult specimens of Terrapene carolina L. were used as controls. Cajal's reduced silver method, Heidenhain's hematoxylin and alum cochineal, Golgi's rapid method, and toluidine blue were employed. Sections were cut in the three planes.

The topography of the somatic motor nuclei of the cranial nerves, nucleus interstitialis, nucleus of the fasciculus longitudinalis medialis, nucleus commissurae posterioris, nucleus interpeduncularis, nucleus reticularis, nucleus motorius tegmenti and nucleus of the raphe, with their fiber connections, is described. The comparative anatomy and possible function of these nuclei are discussed. Tuge concludes that: The ventral part of the hypoglossal nucleus is continuous with the ventral motor columns of the spinal cord and may be considered as a center for the dorsolateral longitudinal muscles of the neck. Small numbers of the root fibers of the oculomotor nucleus are crossed in the dorsal tegmental decussation. The fasciculus longitudinalis medialis in part is continuous with the posterior commissure, in part is continuous with the hypothalamic region and in part decussates in the region of the retro-infundibular commissure. The fasciculus longitudinalis medialis consists of ascending and descending fibers conveying vestibular and optic impulses, possibly also impulses from higher centers. The interpeduncular nucleus is continuous caudally with the parvocellular nucleus of the raphe. The interpeduncular nucleus is recognized as an important relay station for the distribution of impulses, chiefly olfactory, to motor centers of the bulb. Both the nucleus motorius tegmenti and the nucleus of the raphe constitute an apparatus of coordination which has direct relation to motor nuclei. The nucleus reticularis is an apparatus of correlation, having only indirect, or at best, only questionable connection with motor centers.

FRAZER, Philadelphia.

TOPOGRAPHY OF THE NUCLEI OF THE DIENCEPHALON OF THE CAT. W. R. INGRAM, F. I. HANNETT and S. W. RANSON, J. Comp. Neurol. **55**:333 (Aug.) 1932.

The authors have reexamined the thalamus of the cat to fix the nuclear boundaries as definitely as possible, and present a series of illustrations which should be of considerable practical value to the experimenter.

The nuclear groups of the thalamus and hypothalamus of the normal cat have been identified in brains prepared in such a way that sections stained for cells with cresyl violet alternate with sections stained for myelin sheaths by Weil's method. Thus, in the same series, in which all the sections are cut in the same plane, the nuclear topography was studied with relation to the cell groups and to the pattern formed by the myelinated fibers. This material was prepared to furnish orientation charts for use with the Horsley-Clarke instrument, results of which have been published in this journal (ARCH. NEUROL. & PSYCHIAT. **28**:513 [Sept.] 1932).

An attempt has been made to illustrate effectively the nuclear topography by drawings of transverse sections taken at various levels through the diencephalon. For each level a carefully made detail drawing of a section stained by Weil's method is paired with an outline drawing of the next adjacent section stained with cresyl violet, in which the boundaries of the nuclei are indicated. Detailed descriptions of the thalamic nuclei in the cat have previously been given in papers by Rioch and LeGros Clark. Only a brief discussion of each nucleus is given here. The differences in the terminology applied by various authors are mentioned. Some of the nuclei are sharply outlined, but many of them merge with one another by almost insensible gradations. Every criterion has been used whenever possible: type of cells, arrangement of cells, character of ground substance, general texture, fibrous pattern and connections of fibers as far as they could be determined. The authors agree that it will be necessary to know more of functional relationships and connections before the limits to the centers in this region may be permanently defined.

ADDISON, Philadelphia.

HYPERTENSION WITH RETROPERITONEAL GANGLIONEUROMA AND SOFTENING IN THE BRAIN AND SPINAL CORD. FLOYD H. JERGESEN, Arch. Path. **16**:340 (Sept.) 1933.

The region of the suprarenal glands is a common site for the occurrence of a group of neurogenic tumors classified as sympathogoniomas, ganglioneuromas and paragangliomas. These tumors have the same embryologic origin as the suprarenal medulla and the adjacent sympathetic ganglia, namely, the primitive sympathogonia which wander into this region. Divergence in the process of differentiation leads to variation in structure and in function.

The most primitive type of tumor in this group is the sympathogonioma (neurocytoma). It is composed of small round cells, about the size of a small lymphocyte, each containing a deeply staining, round, compact nucleus and a scanty amount of cytoplasm. The paraganglioma (pheochromocytoma) is a more mature type of tumor composed of chromaffin cells resembling those of the suprarenal medulla. These large cells are polyhedral. In sections fixed in Zenker's solution the cytoplasm contains characteristic brown granules. The nuclei are large, stain poorly, are granular and contain one or two nucleoli. The ganglioneuroma is a still more mature neoplastic representative of the primitive stem cell in its divergence and maturation in the direction of the spinal ganglion type of cell.

Paragangliomas have been found in some cases of hypertension, and an etiologic rôle in its development has been suggested.

The case reported is that of a young man who had high blood pressure in the presence of a ganglioneuroma in the vicinity of the left suprarenal gland. Marked arteriosclerosis was present in the kidneys, brain and spinal cord. The brain and spinal cord showed multiple areas of hemorrhagic softening. There was moderate arteriosclerosis in the heart with mild involvement of the arterioles of the lungs, liver, suprarenal glands, pancreas, intestines and skeletal muscles. The left testis was maldeveloped.

WINKELMAN, Philadelphia.

THE NEUROFIBRILLAR STRUCTURE OF THE SEVEN MILLIMETER CAT EMBRYO. WILLIAM F. WINDLE, J. Comp. Neurol. **55**:99 (June) 1932.

The present study is one of a series in which the development of intrinsic structures of the nervous system of the cat embryo is to be described. The embryo measuring 7 mm. represents an early premotile stage. Five embryos of that size were removed from the uteri of two cats nineteen days after mating had been observed and four and one-half days before the time of the earliest motility that has been reported. The Bielschowsky stain and the pyridine silver technic of Ranson were employed. Two embryos were sectioned transversely through the trunk and the other at right angles to the long axis of the rhombencephalon. Reconstructions in cardboard of portions of the neural tube and its attached ganglia were made in order to facilitate the recognition of various parts.

All the motor nerves, both somatic and visceral, arise from a single longitudinal column of neuroblasts located in the ventral part of the basal lamina. Little evidence of subdivision of the motor column is seen. Its diameter increases at the places where various motor roots arise. It is interrupted almost completely between the oculomotor and trochlear nerves. All of the motor nerves except the trochlear have made their exit from the neural tube and, at least, the rostral have reached their respective premuscle masses.

The primordia of all the sensory ganglia are present. Anlagen of the mesencephalic and spinal tracts of the trigeminal and the spinal vestibular nerves and of the tractus solitarius have appeared.

The mechanism of association is formed by neurons of the second order, which form two primitive longitudinal pathways, a ventral and a lateral. These pathways contain the primordia of the fasciculus longitudinalis medialis and possibly those of the tectobulbar and reticulospinal tracts. The sympathetic nervous system is represented by poorly developed neuroblasts in close proximity to the aorta and viscera, and the anlagen of the ciliary ganglia.

ADDISON, Philadelphia.

PRENATAL DEVELOPMENT OF BEHAVIOR IN THE ALBINO RAT. A. W. ANGULO Y GONZALEZ, J. Comp. Neurol. **55**:395 (Aug.) 1932.

This study was carried out on 643 fetuses obtained from 77 litters. They ranged in age from 14 to 21 days (term). The first sign of motility was found at fifteen days and eighteen hours after insemination. The movement consisted of a slight bending of the head, involving only the region of the neck and taking place only after stimulation of the region of the snout. The snout came closer to the stimulator and hence this was not classified as an "avoiding reaction." Spontaneous activity was observed in several fetuses 16 days old. In the older fetuses motility spreads in the cephalocaudal and proximodistal direction. Thus, the movement progresses so as to involve first the forelimbs, later the rump and finally the hindlimbs. During the first stages of development the appendages move only with the trunk. This reaction of the total mass is called a "total pattern reaction." The total pattern reaction consists of a primary or basic movement, lateral flexion of the trunk and a series of secondary movements. Similarly there develops later a total pattern consisting of a basic movement of extension of the head and a series of secondary movements. During the later period of development of fetal behavior a number of specific reflexes show what at first seems to be a breaking up of the total patterns into individual and specific reflexes. However, Angulo believes that the process by means of which the individuation and specificity of certain reflexes are attained is not a disintegration or breaking up of the established pattern, but an inhibitory action by means of which the primary movements are in a large measure arrested. In other words, the total pattern reaction is never abolished completely; nor is the dominance of the primary on the secondary movements lost.

The discussion of questions arising from the results of this investigation, with references to the work of others on kindred subjects, has been deferred to a later time.

FRASER, Philadelphia.

CONNECTIONS OF THE AUDITORY CORTEX OF THE CAT. FRED A. METTLER, J. Comp. Neurol. **55**:139 (June) 1932.

In the light of recent doctrines of the generalized nature of the cortex, Mettler describes the effect of removing various parts of the cortex throughout the region generally ascribed to audition in an animal sufficiently developed to show cortical specialization. Under ether anesthesia, the cortex was removed mechanically with a small curet. After all bleeding had ceased, the clots were removed and the dura, bone and skin replaced. At the end of eleven days the animal was narcotized with chloroform and bled to death from the heart. The skull case was opened immediately and the brain in situ was douched with neutral formaldehyde and subsequently prepared by the Marchi technic for degenerated fiber connections.

In all cases short association fibers to special parts of the surrounding cortex are degenerated. There is invariable collosal association to the opposite cortex, though the majority of the callosal fibers go to an area of the opposite hemisphere corresponding to the site of the lesion. Any point (in the ablated areas) is related not only to a corresponding crossed cortical point but with a large area corresponding to, though not so extensive as, the homolateral zone of short association. In all cases projection fibers were found. These differed according to the site of the lesion and fell into three groups: (1) cerebropontile fibers, which arise from any of the ablated areas; (2) cerebrotectal fibers, which go to the intermediate stratum of the superior colliculi by means of a direct capsular route, and (3) cerebrotegmental fibers, which go to the superior colliculi by way of a tegmental route. In retrograde preparations the homolateral median geniculate body shows marked degeneration following injury to the cortex in the regions of the sylvian fissure.

ADDISON, Philadelphia.

THE STRUCTURE AND CONNECTIONS OF THE THALAMUS. W. E. LE GROS CLARK, Brain **55**:406 (Sept.) 1932.

The importance of the study of the thalamus may be based on the facts that as far as the purely sensory functions of the neopallium are concerned, they are dependent on the thalamus, and that the thalamus is the anatomic equivalent of the very threshold of consciousness. One of the main objects of this paper was to clear the terminologic atmosphere. From the point of view of comparative anatomy, the structure of the thalamus is described in detail under the headings of the evolution of the thalamus, general nuclear configuration of the mammalian thalamus, the ventral group of nuclei, nucleus medialis ventralis, the anterior group of nuclei, the relation of the optic tract to the diencephalon, the pretectal nucleus, the median geniculate body, the lateral group of nuclei, the central median nucleus and the dorsomedial nucleus. An interesting concept is presented. that the hypothalamus is related to the visceral activities of the vegetative function through its relations to the pituitary gland. It seems to be an essential element in the integration of the emotional reactions and in the psychogenesis of emotional experience. The dorsal part of the thalamus forms an elaborate center of sensory correlation for the reception of external stimuli. An awareness of objective phenomena is thus mediated. The periventricular system of fibers and interstitial nuclei may be regarded as a link between these two parts (hypothalamus and dorsal part). Finally, the dorsomedial nucleus occupies a significant position, an intermediate station through which the whole periventricular system can be brought under the dominating influence of the frontal cortex.

MICHAELS, Boston.

A STUDY OF 300 INMATES OF A STATE FARM. CHARLES S. RICKER, J. Juvenile Research **16**:102 (April) 1932.

The majority of the prisoners at the Massachusetts State Farm are below normal mentally (intelligence quotient below 75), single, unskilled in any trade and

from homes seriously below standard economically, socially and culturally. The men had an average of ten arrests each. The ultimate disposition seemed to be custodial in about half the cases, and was presumably so in many others. So far as a causative factor can be evaluated, most of the inmates appeared to owe their difficulties to inadequate domestic training. In the middle-aged men whose delinquencies did not begin until that period in life, marital infelicity seemed to be a potent factor. Basically, however, the delinquency rests on a defect in the instinctive emotional machinery of the subject and not on intellectual inadequacy. Ricker has a suggestion for management in these cases. So-called "bad" habits are really normal childish or infantile responses carried over into adult life; the trouble has been a failure of the person to modify these habits to suit his maturing responsibilities. If it were possible to measure the modifiability of behavior so that those whose adapting mechanisms were defective and unstable could be found and isolated, one could treat the problem of delinquent behavior at its very roots.

DAVIDSON, Newark, N. J.

THE LATENT PERIOD OF SKELETAL MUSCLE. J. ROOS, J. Physiol. **74**:17 (Jan. 14) 1932.

The duration of the latent period has become of great importance for the comprehension of muscular contraction and of the relation between the phenomena accompanying it. Roos reviews previous work in this field and describes experiments performed to measure this period, using the gastrocnemius muscle of the frog. The results were as follows: The latent period is shorter than 0.4 σ; the opinion that the electrogram precedes the mechanogram is untenable; the theories that the latent period coincides with a determined part of the action current and with the absolute refractory phase are untenable; it is likely that action current and mechanogram develop simultaneously; the beginning of the mechanogram exhibits two phases, an initial and a following phase. If their difference is produced by an increasing resistance in muscle against the alteration of form, its time relations correspond with the increase of viscosity and elasticity established by Gasser and Hill. In that case muscle force develops in the first ten thousandths of a second. It is not probable that the increase of viscosity and elasticity found by Gasser and Hill is related to the latent period in the way they suggest.

ALPERS, Philadelphia.

DEVELOPMENT OF THE NUCLEI AND TRACTS OF THE MIDBRAIN. RALPH F. SHANER, J. Comp. Neurol. **55**:493 (Aug.) 1932.

This is a study of the formation of the chief nuclei and tracts in the brain of the pig embryo as revealed by closely graded series of sections stained with toluidine blue or by Cajal's technic. Wax models of the brains were made and then graphic reconstructions based on the models.

The primitive midbrain is seen to be made up of the central gray matter and nuclei of cranial nerves, with the mesencephalic root of the fifth nerve and the spinotectal tracts as afferent paths and the tectospinal tract as an efferent path. The superior colliculi take up nearly all of the spherical dome of the original midbrain. The inferior colliculi are formed within dorsolateral bulges of the roof which appear secondarily in embryos measuring about 20 mm. Differentiation within the red nucleus begins with the appearance of large motor cells at the caudal pole of the nucleus and with the invasion of the dentatorubral tract. There is extensive development of the system centering around the mamillary nuclei, but its relation with the mibrain is not apparent. The last important additions to the midbrain are the pyramidal tract and the substantia nigra. Both are superimposed on the primitive midbrain.

FRASER, Philadelphia.

THE EFFECT OF INJECTIONS OF EXTRACTS OF ADRENAL CORTEX ON THE DEVELOPMENT AND SEX FUNCTIONS OF THE ALBINO MOUSE. R. A. CLEGHORN, J. Physiol. **76**:193 (Oct. 4) 1932.

The work described by Cleghorn constitutes a further attempt at the experimental elucidation of the averred relationship between the suprarenal cortex and the gonads, using extracts of suprarenal cortex. He found that the final average weight of young female mice, which for a period of four weeks received daily injections of extract of suprarenal cortex made according to the method of Sivengle and Pfiffner, was 8.7 per cent greater than that of the controls. There was no observable difference in the final average weight of test and control males. The final average weight of the testes of the test males is 8.3 per cent less than that of the controls. These differences in weight are not held to be significant. The injection of this type of extract has no appreciable influence on the age of maturation of young female mice, as judged by the opening of the vagina, nor has it any specific effect on the sex function of the adult female mouse, as judged by its effect on the estrous cycle. The injection of a watery extract of beef suprarenal cortex does not cause the cessation of estrus, and the frequent prolongation of the diestrous interval that follows such injection can be attributed only to nonspecific influences.

ALPERS, Philadelphia.

PERSONAL IDENTIFICATION BY ELECTROCARDIOGRAPHY. ISRAEL CASTELLANOS, J. Crim. Law & Criminol. **23**:356, 1932.

The author considers the possibility of using the electrocardiograph as a means of personal identification. He contrasts it with the method of finger printing as follows: The electrocardiograph is expensive, is not easily portable, and requires many precautions in its operation. The electrocardiogram must be made by an expert or special operator. The electrocardiographic method is expensive, even when the most simple apparatus is used. No system of classification for the individual electrocardiogram has thus far been evolved. The electrocardiographic method permits a wide margin of errors. The electrocardiograph can be used only for the living subject as it requires the functioning of the heart. The electrocardiogram is alterable by disease and by the will of the subject. Castellanos concludes that electrocardiography is suggestive, impressive and most useful in the clinic, but that the papillary print remains the method of personal identification without a peer.

PEARSON, Philadelphia.

A CASE OF PORENCEPHALIC IMBECILITY. RICHARD J. A. BERRY and R. M. BATES, Brit. M. J. **1**:830 (May 7) 1932.

Clinically, the case of a patient, aged 27, appeared to be one of imbecility complicated by chronic nephritis. One year before death she had several convulsions followed by right hemiplegia. There were signs of chronic nephritis at that time. This seemed to improve somewhat, but a few months before death there was an exacerbation. Death followed from uremic coma. Postmortem examination revealed advanced chronic nephritis and fibrinous pericarditis. There was marked porencephaly, the right cerebral hemisphere being less involved than the left. No lesion was discovered to explain the paralysis-producing lesion. In the light of modern embryologic knowledge, the porencephaly was due to an arrest of cortical development in the telencephalic neural wall occurring at, or about, the sixth week of intra-uterine life.

FERGUSON, Niagara Falls, N. Y.

ATHETOSIS. PAUL C. BUCY and DOUGLAS N. BUCHANAN, Brain **55**:479 (Dec.) 1932.

After reviewing various concepts, Bucy and Buchanan state that there is evidence to show that athetosis is effected by impulses from the cerebral cortex via an extrapyramidal motor system, and that removal of the cortex (area 6 *a a*) or section of these extrapyramidal pathways will abolish such movements. The

case of a girl, aged 7, with an undetermined cerebral disease, left hemiparesis, athetosis of the left arm and left-sided epileptiform attacks, is described. Typical athetoid movements were elicited from a definite area of the exposed cerebral cortex. The athetosis disappeared following excision of this area. It was concluded that the athetoid movements were effected by the area 6 *a a*, of heightened irritability, and was possibly freed from higher (inhibitory) control by degeneration of transcortical connections and that this area produced its effect by efferent impulses which passed via subcortical (extrapyramidal) centers to the spinal cord and the anterior horn cells.

CATAPLEXY. MAX LEVIN, Brain **55**:397 (Sept.) 1932.

The author has found more than 180 cases of Gelineau's syndrome recorded, but only 14 patients suffering from cataplexy and free from morbid somnolence have been noted. Two interesting cases of "cataplexy only" are presented. The first patient, a Negro woman, had rheumatic-arthritic-cardiac symptoms, gonadal inadequacy and nervous symptoms consisting of cataplectic attacks, attacks of unconsciousness and a residual tremor of the upper right extremity. The second patient, a white man, of a manic-depressive disposition, was subject to attacks of cataplexy localized to the right arm and hand; later, he had apparent attacks of epilepsy. The first case, suggesting a striatal lesion, is of interest from the point of view of Redlich, who emphasizes the tone-regulating function of the striatum, and the theory of Rothfeld, that the striatum is capable of being inhibited by the thalamus.

PHARMACOLOGY AND THE GRASP REFLEX. CURT P. RICHTER and ARTHUR S. PATERSON, Brain **55**:391 (Sept.) 1932.

The grasp reflex was elicited in adult monkeys with bulbocapnine, carbon dioxide, ether, chloroform, amytal, paraldehyde, alcohol, phenobarbital, scopolamine, cocaine, morphine, apomorphine hydrochloride, camphor, insulin, chloral hydrate, physostigmine and strychnine. The depressants may paralyze the mechanism in the frontal lobes. The fact that the reflex is brought out by hypnotics which are thought to act chiefly on the mechanism of sleep in regions around the third ventricle is suggestive of their involvement of the nervous system at a fairly low level. Epinephrine, atropine, pilocarpine hydrochloride, extract of posterior lobe of the pituitary gland, caffeine, glyceryl trinitrate and histamine failed to elicit the reflex.

RELATION OF THE FRONTAL LOBES TO POSTURE AND FORCED GRASPING IN MONKEYS. J. F. FULTON, C. F. JACOBSEN and MARGARET A. KENNARD, Brain **55**:524 (Dec.) 1932.

Complete bilateral destruction of the frontal areas in monkeys produces no permanent alteration of posture and no motor deficit in the extremities. When, in addition, the premotor areas are removed, forced grasping and groping (preseveration), slowness of movement and a torpid mental state appear. When the complete premotor area is removed forced grasping is elicited. Simultaneous extirpation of the motor and premotor areas causes a less flaccid paresis with the appearance of forced grasping. It is thought that the so-called postural disturbances associated with frontal lesions in man are undoubtedly caused by involvement of the premotor area.

SYPHILIS OF THE NERVOUS SYSTEM IN THE SUDANESE. T. F. HEWER, Brain **55**:537 (Dec.) 1932.

The lack of reliable data on natives in the tropics prompted the present study of 400 syphilitic Sudanese. The Kahn test gave a positive reaction in 31 per cent of 420 apparently healthy prisoners. The incidence of neurosyphilis was found to be 6.75 per cent in the present series. The absence of parasyphilitic involvement in the Sudanese is best explained as a result of an actual cell immunity acquired in the early stages of the disease.

MICHAELS, Boston.

Society Transactions

NEUROLOGIC SOCIETY OF PARIS

Twelfth Annual International Neurologic Assembly, Paris, May 31-June 1, 1932

M. Levy-Valensy, *President*

(Revue neurologique **1**:1041 [June] 1932) Abstracted by Walter Freeman, M.D., with the Assistance of Edna Caspari, Washington, D. C.

Modern Etiologic Conceptions of the Epilepsies. Jean Abadie.

Evidence of a firm belief in the heredity of epilepsy is found throughout ancient literature, and physicians through the centuries have sought to prove it by statistics and experiments. When bitterly assailed, they sought refuge in the theory of an "epileptoid constitution," which was explained as a fundamental and congenital mental disposition, the expression of a biologic constitution which is transmitted by heredity and presents an ensemble of modalities, the dominant ones of which are always identical, even in persons free from the disease but belonging to an epileptic family. Near the beginning of the twentieth century Pierre Marie brought forth the idea of an "epileptic syndrome" in opposition to the old belief in idiopathic epilepsy. Common epilepsy, so long believed a hereditary nervous condition without permanent physical cause, was taught by him to be the result of encephalic lesions of variable nature and origin, the existence of which may be affirmed even when the lesions are not directly evident. Common epilepsy is not constitutional and innate; it is acquired and personal. It is a syndrome that may appear under very different conditions but that constitutes by its aspect and habitual evolution a clinical entity. It has no autonomous existence, because it always depends on alterations of the central nervous system, which are more or less manifest but always definitely organic. Whether epilepsy appears in infancy, middle age or old age, it is always the result of these pathologic changes.

In the child, the causes of these lesions must be sought in the obstetric accidents and toxic infections of infancy. The convulsions of infancy, however, though similar to epileptic seizures, are to be considered only as sharp convulsive attacks due to involvement of the nerve centers, occurring unexpectedly under the influence of diverse, frequently hidden causes. This sharp convulsive syndrome should never be mistaken for the first appearance of chronic epilepsy. It is peculiar to the first months or years of life. Its character of sharp, primordial evolution is best expressed by the term "eclampsia" or "infantile eclamptic syndrome." All infants with eclampsia are not destined to have epilepsy, but epilepsy may develop from infantile eclampsia, either immediately by insensible transitions or after an indefinite period of latency.

Hereditary syphilis is an etiologic factor of epilepsy in children in the sense that it is more capable than other infantile infections of provoking lesions essentially epileptogenic in nerve centers. Acquired syphilis has long been considered one of the most frequent causes of epilepsy in adults. Moreover, since the aggravation of epilepsy by intercurrent infectious diseases is frequently observed, why should not syphilitic infection by its affinity for the nervous system aggravate epilepsy? The rare cases of epilepsy due to secondary syphilis that have been observed (twenty in the last sixty years) call for more study and research to clear up the possible relation of this form of epilepsy to the latent meningitic lesions found so

frequently during the secondary period of syphilis. Epilepsy due to tertiary syphilis, the individuality and frequency of which are clearly established, may be described as an epileptic form of cerebral syphilis. Its true nature is best demonstrated by its curability under antisyphilitic treatment, which sometimes acts rapidly but more often only after patient and prolonged application. Epilepsy due to parasyphilis is never accompanied by symptoms of cerebral syphilis. It is permanent and resists all antisyphilitic treatment. Most authors prefer to call this form of epilepsy "late syphilitic epilepsy."

Epilepsy following malaria therapy may appear in different forms, even in the grave and pernicious form of paludism; numerous examples are known in which quinine alone or associated with antiepileptic remedies has caused singular improvement. There is no justification, however, for accusing the induced malarial infection exclusively of provoking the epileptic crises that frequently occur during treatment of dementia paralytica. Any fever therapy, and particularly malarial treatment, transforms the diffuse process of syphilitic meningo-encephalitis into a more acute process of tertiary cerebral syphilis, that is, lesions more specifically exudative and more responsive to antisyphilitic treatment. This gives rise to the hypothesis that the epilepsy observed after malarial therapy is merely a clinical expression of a transformation of lesions, the focal character and location of which, more than their nature, explain the provocation of convulsive attacks. Recent observers have reported the unforeseen appearance under the influence of malarial therapy of lesions typical of tertiary syphilis, such as gummas of the pharynx, tonsils, tongue and skin. Under these conditions epilepsy following malarial therapy is merely a therapeutically provoked variety of epilepsy due to syphilis. However, before final judgment is given new facts must be studied.

Dagonet stated that meningitis, convulsions and epilepsy constitute the three most dangerous legacies of alcoholism in the forebears. Other authors have given to hereditary alcoholism the primordial rôle in the genesis of common epilepsy. Epilepsy due to alcoholism in the parents, more than any other type, shows mental disorders, modifications of character, psychic equivalents and a more rapid dementia. This form of epilepsy is also distinguished by its frequent association with microcephalia and with a state of constitutional deficiency of intellect—idiocy, imbecility and mental debility. It is particularly resistant to the usual methods of treatment of epilepsy.

The lack of an actual relationship between hysteria and epilepsy seemed well established when, owing to the great number of convulsive crises observed during the World War, the discussion was revived. It now seems established, however, that there is no identity of nature between hysteria and epilepsy. One finds both conditions in the same person, but one is not derived from the other; especially, epilepsy never develops from hysteria by way of aggravation or transformation. In certain unusual cases, hysteroid elements may be found in epileptic crises and epileptoid elements in hysteric crises, but they are only chance occurrences and not essential phenomena. The difficulties of the differential diagnosis of the two conditions will not resist prolonged and attentive observation.

Perhaps the most frequent cause of epilepsy is traumatism. The World War brought a considerable contribution to the knowledge of traumatic epilepsy from a clinical and pathogenic as well as from a therapeutic point of view. According to different but concordant statistics, epilepsy occurred in from 10 to 20 per cent of the persons who received wounds of the head or brain during the war. According to some authors, the incidence may have been even greater, perhaps as high as 50 per cent.

Epilepsy is more frequent after early or late surgical intervention, especially after those operations in which owing to their repetition and extent there is danger of causing new damage to the meninges and the brain, thus increasing the primary havoc caused by the wound and producing tardy complications, such as prolonged suppuration and cerebral rupture. Obliteration of the wound by cicatricial ossification of the bony breach and cranioplastic operations facilitate the development of epilepsy, while foreign bodies in the brain, above all projectiles

embedded at a high speed, are relatively well tolerated and epilepsy may not develop until after the operation for extraction of the foreign body. Ligation of the great vessels of the neck is reported as greatly favoring the development of epilepsy. Injuries to the parietal, frontal, temporal and occipital lobe are inclined to cause epileptic crises. Lesions of the rolandic zone are responsible for four fifths of the cases of traumatic epilepsy, but wounds of the cerebellum do not appear to be epileptogenic. Late Bravais-Jacksonian epilepsy is most frequently due to delayed meningeal or cerebral abscesses, to secondary meningeal hemorrhages, to pseudocystic serous meningitis and to an encephalic evolutive process with disintegration and interstitial hemorrhages.

Special treatments have been developed with the idea of decreasing the epileptogenic effect of meningocerebral scars. High voltage roentgen therapy has been thought useful by some; electro-ionization of the cerebral wound before surgical intervention is advocated by others. In 1929, transcerebral calcium electrolysis was reported as the best preventive of corticomeningeal scarring, the most frequent generator of traumatic epilepsy.

Sauvages, in 1772, first recognized a special form of "uterine epilepsy" which he called the eclampsia of parturition, but not until the nineteenth century was a distinct separation made between puerperal eclampsia and common epilepsy. Today, eclampsia is considered merely as a sharp epileptic syndrome of the toxemia of pregnancy, the origin of which is found in the toxic substances secreted by the embryo, which act on the maternal organism, creating renal and hepatic lesions. The maternal mortality as recorded in the literature averages from 15 to 25 per cent; the fetal mortality, about 33 per cent. The statistics of obstetric clinics are generally more favorable, showing a mortality of from 5 to 15 per cent for the women and from 10 to 20 per cent for the children. A rise in temperature always accompanies an eclamptic attack; the elevation is maintained during the intervals, with a new rise at each recurrence; thus it sometimes rises to 40 or 41 C. (104 to 106 F.). Such persistence of fever is a grave prognostic sign; on the other hand, a decrease in temperature sometimes precedes the cessation of attacks and announces amelioration. The measure of arterial tension is of considerable importance for anticipating eclamptic attacks and for judging the prognosis. Arterial hypertension precedes an eclamptic attack and may even appear before albuminuria. The constant watchful care now given all persons with eclampsia has caused the disease to lose more and more its ancient character of relatively frequent attacks and redoubtable gravity.

For a long time epilepsy has been dreaded in connection with pleural irritation set up by simple exploratory punctures or as the result of thoracocentesis. Sometimes during lavage of the pleura or after the injection of medicinal substances into the pleural cavity, epileptic convulsions have suddenly appeared which could not be attributed to the quality or the quantity of the fluid introduced. The current practice of gaseous insufflations has permitted the observation of new facts. Clinical descriptions of pleural epilepsy may be summed up thus: In the first group of cases it is an exaggeration to speak of true epilepsy. The symptoms observed consist merely in a syncopal state, more or less grave, accompanied by convulsions of the epileptic type. This state may prove fatal in about one third of the cases. In the second group, attacks of epilepsy occur, which in some instances have all the clinical characteristics of common epileptic attacks and in others resemble Bravais-Jacksonian seizures. In the third group, which is most rare, the initial convulsive attack is followed by a prolonged loss of consciousness, during which convulsive attacks are repeated at intervals until they become subintrant, whereupon death usually occurs after several hours, though in exceptional cases the patient may live for from two to three days. The gravity of pleural epilepsy is such that a fatal termination has been noted in three fourths of the cases.

The pathogenesis of pleural epilepsy has always piqued the curiosity of those who have observed it. Many theories have been advanced, but all have been abandoned except two: the theory of reflex pleural irritation and the theory of

embolism. According to the theory of reflex excitation, the initial pleural excitation causes simultaneous pulmonary and encephalic vasoconstriction, productive of the convulsive state. The gravity of the attacks depends more or less on the susceptibility of the pleura. According to the theory of embolism, pleural epileptic attacks are caused by bubbles of air or gas, introduced by the injection into the gaping veins of the inflamed focus of the pleura or the lung, thus forming gas emboli as far as the arteries of the brain. How, then, can one explain the occurrence of spontaneous pleural epilepsy analogous to that reported in 1931 by Roch which developed in an unrecognized case of serofibrinous pleurisy in which there was no fever and in which there had been no intervention on the pleura?

Pleural epilepsy is an extremely rare form of epilepsy. The epilepsy arising from therapeutic pneumothorax, in particular, is observed only exceptionally, if one considers the small proportion of these cases in relation to the large number of gaseous insufflations done at the present time. The possibility of epilepsy should not influence the physician in his decision to create a therapeutic pneumothorax, though its unforeseen occurrence and its frequent gravity are always to be feared. Attacks of epilepsy have not been observed during the surgical production of pleuropulmonary collapse, in spite of the number of similar operations practiced. No one has reported the occurrence of epilepsy during phrenicotomy, even after pleural attacks, during intrapleural or extrapleural pneumonolysis or during thoracoplasty with or without pleural complications.

By the term cardiac epilepsy is implied epileptic manifestations that appear following cardiac disturbances and which were caused directly or indirectly by them. Two different types may be distinguished: permanent bradycardiac epilepsy and asystolic epilepsy. Permanent bradycardiac epilepsy is one of the constituent elements of the Stokes-Adams syndrome. It may appear as vertigo or as convulsive crises. The epileptic attacks always correspond to a paroxysmal slowing of the pulse, either spontaneous or provoked. Bradycardiac epilepsy is benefited by all therapy that modifies the cardiac rhythm. It is due to encephalic ischemia provoked by pauses of ventricular contraction. Today no one contests the existence of bradycardiac epilepsy. This form of epilepsy is found not only in the Stokes-Adams syndrome but in the temporary bradycardiac or paroxysmal states and the latent disturbances of cardiac rhythm, such as may be seen in certain types of intoxication or during convalescence from infectious maladies. One should remember the gravity of bradycardiac epilepsy and the danger of a fatal termination that accompanies all crises, even the slightest. Gallavardin's rule should always be followed: Sudden death should be foreseen, but not foretold.

Asystolic epilepsy has been reported in persons with various types of cardiopathy—valvular, aortic and mitral lesions, chronic myocarditis and even callous mediastinopericarditis. It is never associated with well compensated cardiac lesions and appears only in transitory periods of cardiac insufficiency or at the terminal asystolic phase. It has been observed almost exclusively in adults and aged persons and is exceptional before the age of 40. Asystolic epilepsy is looked on as of particular gravity because of the possibility of death during an attack as a result of heart failure suddenly provoked by the crises, of a cerebral "stroke" or of the sudden and rapid evolution of terminal asystolia.

At the end of the nineteenth century, epilepsy of the aged was distinctly separated from the epilepsy of adults and was individualized under the term "senile epilepsy." Senile epilepsy may be separated into two distinct groups: epilepsy of sexual involution, i. e., presenile epilepsy, and epilepsy of confirmed senility, or senile involution. The published facts concerning the influence of age on epilepsy are rare; they treat almost exclusively of the influence of the menopause in provoking epilepsy in women. Menopausal epilepsy appears as a special form, generally transitory, and shows a tendency to spontaneous recovery.

Does epilepsy of sexual involution occur in the male? Its existence may be doubted, considering how few reports there have been on epilepsy with pathologic changes in the testicular secretion and on the influence of the male glands on epilepsy. However, all those who have examined a number of epileptic persons

have observed examples, rare but definite, of epilepsy suddenly developing in men about the age of 50 under the following conditions: A man presenting the appearance of good physical health, without any sign of a psychosis in evolution, without the least epileptic antecedent and without any modification of his virile capacity, is suddenly attacked by an epileptic crisis, or more often by an equivalent motor attack, without a special provocative cause. Such attacks occur more or less periodically at variable intervals. At times the epileptic manifestations are limited to one or more rare paroxysms. The attacks may become less frequent and cease even without antiepileptic treatment. This form of epilepsy in men, though exceptional, resembles the epilepsy of the menopause in more than one trait. It is like it not only in the age at which it appears but in its transitory form and its tendency to spontaneous recovery.

True senile epilepsy appears mostly in persons over 60. It occurs with equal frequency in men and women but is much rarer than epilepsy in adult life and in youth. Senile epilepsy, considered in its habitual manifestations, resembles in all points the epilepsy of infancy and adolescence. Certain physicians ascribe to it a special prodromal phase; but these prodromes of senile epilepsy have no distinct value either in their frequency or in their characteristics; they indicate merely the parallel evolution of cerebral disorders due to senility and independent of epilepsy. The characteristic that best individualizes senile epilepsy is the frequent presence of mental disorders showing a progressive dementia which is more rapid and wholly different from ordinary epileptic dementia.

Senile epilepsy does not show constant anatomic alterations. The lesions differ in various cases. Those that occur most frequently are of two kinds: The first type consists of old lesions of tertiary syphilis which appear as meningitic, sclerotic or sclerogummatous plaques of cicatricial or retractile tendency. These lesions, according to some authors, produce one of the most tenacious varieties of senile epilepsy, which is distinguished by the persistent presence of violent headaches. It may begin as a Bravais-Jacksonian type and then rapidly change into generalized attacks. The second type, which has occurred in the greater number of the cases studied, consists of arteriosclerosis and cerebral atheroma. In these cases arteriosclerosis has acted differently, sometimes through diffuse lesions, both cerebral and visceral, sometimes by focal cerebral disintegration and sometimes by progressive lacunar cerebral sclerosis. Aside from these lesions most frequently observed, Léri, has reported a certain worm-eaten state of the brain associated with pronounced dementia. Miliary sclerosis of the cerebral cortex not directly related to arteriosclerosis was observed in a few cases. Such lesions are always accompanied by epilepsy.

Anatomically, two forms of senile epilepsy are distinguished. The first, cardiovascular senile epilepsy, shows generalized atheroma and great cardiac disturbance. The second, senile epilepsy with arteriosclerotic foci, shows Bravais-Jacksonian attacks or generalized convulsions with strong unilateral predominance. Epilepsy is relatively rare in senile dementia and appears chiefly in the final period, when it presents the usual signs of common epilepsy. The dementia of senile epilepsy is caused by the lesions of cerebral sclerosis, superficially diffuse, with profound alterations of the tangential fibers, and by the foci of sclerosis in connection with cerebral atheromatosis. Senile epilepsy in general may be the result of any of the sclerotic encephalitides due to cerebral arteriosclerosis, but the lesion most likely to cause epilepsy is diffuse superficial cerebral sclerosis. As may be seen, the question of senile epilepsy requires further research because it is far from a definite solution.

RECENT ADVANCES IN THE KNOWLEDGE OF THE PATHOLOGIC PHYSIOLOGY AND PATHOGENESIS OF EPILEPSY. P. PAGNIEZ.

Important as neurologic lesions may be, studies and experiments convince one that humoral activity is necessary in the pathogenesis of epilepsy. Interesting alterations in the circulatory phenomena of the brain have been found to precede and accompany epileptic crises. The presence of anemia has been established in

the majority of cases. Vasoconstriction at the level of the cortex and in the pia mater has been observed at operation by a number of authors.

Moreover, local spasms of the blood vessels have been observed in a number of instances before and during attacks. A spasm may even appear in an isolated state as an epileptic equivalent. Is not such a spasm followed by dilatation of the vessels, and may not this alteration be the true epileptogenic factor? Certain experimental facts at least permit this supposition. One must, however, assume the existence of some special factor, such as the duration or alteration of the phenomena, to understand the epileptogenic value of the spasm, because the absence of convulsive attacks in syncope and at the moment of a sudden obliteration of a cerebral vessel by embolism show that anemia alone does not suffice to produce convulsions. Modifications of the cerebral circulation at the moment of a convulsive attack are incontrovertible, but how can one interpret these disturbances? It was supposed that circulatory disturbances might act by producing anoxemia. Lennox showed that attacks could be provoked in certain patients by diminishing the amount of oxygen in the air they inhaled, as well as by inducing hyperpnea. These facts were contradicted, however, by the researches of Teglbjaerg, who succeeded in provoking seizures in this way in only four of fifty patients. Cellular edema, disturbance of ionic equilibrium and variations in the hydrogen ion concentration of the nerve tissue have been suggested as causes at various times, but so far they are purely hypothetic.

Profound ignorance still exists concerning the intimate nature of the nervous symptoms. One might mention hyperexcitability, explosive reactions, etc. Consideration should be given to the theory of inhibition suggested by Jackson, which attributes the nervous symptoms to inhibition of the cortical centers caused by a reflex excitation. When of short duration this inhibition manifests itself in absences, loss of consciousness and amnesia. If of longer duration, it is expressed by vertigo. If still more lasting and more profound, it may produce a complete epileptic attack in which tonic and clonic symptoms occur as a result of the suspension of the restraining action of the cortex on the subcortical and medullary centers.

The development of epileptic attacks, especially of severe crises, thus appears to be dependent on circulatory disturbances that manifest themselves primarily as vascular spasms. The appearance of these phenomena is governed by causes that are apparently extracerebral.

There exist in the epileptic patient a characteristic lack of balance and instability of the vagosympathetic nervous system. This instability is expressed most frequently as vagotonia, which appears in a measure to favor the production of epileptic paroxysms. Probably this activity of the vagosympathetic system is merely the expression of a glandular or humoral disorder; it is not likely that the epilepsy is caused by a primary malady of the neurovegetative system, an essential dystonia.

The belief in the rôle of a humoral factor in the genesis of epileptic attacks has during the last fifteen years instigated a number of researches in which nearly every constituent of the organism has been studied with that theory in view. Nitrogen metabolism has been most carefully examined. The statements of eight different authorities show that though an abnormally high amount of urea is sometimes found, the reported variations are most frequently within the limits of normal. Similar results have been obtained for uric acid. The reports on ammonia in the blood of epileptic patients are about evenly divided. It has been thought that an abnormal protein element might be active in epilepsy, and Cunéo devoted considerable time to the study of albumose in the blood of epileptic patients during paroxysms. The metabolism of lipoids has been studied very little. The cholesterol content has been found to vary greatly. Lennox concluded that there is no connection between the variations in the blood sugar and the production of crises, and Petersen and Schon found a normal amount of dextrose in 78 per cent of 166 examinations. However, a study of the blood sugar curve after the ingestion of sugar and after injections of epinephrine showed abnormal reactions in a number of epileptic patients.

Among the mineral elements in the blood, calcium has received special attention because of its main rôle in normal physiologic balance and in disturbances of neuromuscular excitability. Studies of the calcium equilibrium in epilepsy have given unsatisfactory results as to the total calcium content. Jorgen Madsen, in a recent article based on sixteen cases, reported that he found regularly in persons with epilepsy a normal level of calcium, potassium and sodium in the serum, with a tendency to low normal values. The level of calcium rose immediately before the attacks. Lennox and Allen found average levels of calcium in the serum of seventy-seven persons with epilepsy. Variations in the level of ionized calcium have been recognized for a number of years, and Bigwood estimated that in essential epilepsy the crisis is preceded by a fall (which may reach 32 per cent) in the level of ionized calcium in the blood.

Research on the molecular constituents of tissues in epilepsy, particularly nerve tissues, is still rudimentary. There is little to cite on this subject, except a few studies on the amount of sodium and a work by Blum and Brown on a possible increase of chlorine in the gray substance of the hemispheres. The amount of albumin slowly increases between the attacks. Frisch and his collaborators laid great stress on the increase of albumin in the serum of epileptic patients, which causes a modification of the albumin-globulin relation. Inversely, all circumstances under which the epileptic paroxysms diminish or disappear (intercurrent diseases, therapeutic actions, etc.) are accompanied by an increase of globulin. The amount of fibrinogen was found to be increased in one third of one hundred cases, but no relation was established between these modifications and the repetition of the paroxysms.

Attention has been directed recently to variations in the acid-base balance of the blood and to certain anomalies in the metabolism of water which have been looked on as factors favoring epileptic attacks. It is still too early to reach a decision, but certain facts of interest have been observed. Studies of the blood and urine have shown frequent alteration of the acid-base equilibrium in the direction of alkalosis. Bigwood found in cases of essential epilepsy a remarkable instability of the acid-base equilibrium, with a sharp tendency to alkalosis. This was most marked before the crises, when it was nearly constant. Jarloev observed hyperalkalinity before a crisis but a high hydrogen ion concentration after the attack. Mördre and others also reported alkalosis and, with Bigwood considered whether conditions that favor alkalosis may not favor also the action of a toxic substance or a convulsing process, itself the cause of the attacks. Many authors have studied the hydrogen ion concentration and the ammonia content of the urine. The studies confirm the observation that the reduced ammonia content presents constant irregularities in persons with epilepsy at the time of attacks as well as during the intervals.

Recent observations show that the repetition and occurrence of convulsive paroxysms are in direct relation with the degree of hydration. American works on the effect of therapeutic dehydration of epileptic patients show notable progress. McQuarrie and Temple Fay found that reduction of the total intake of water to about 400 cc. a day results in a considerable decrease in the frequency, and even disappearance, of attacks. Indirect confirmation of these results may be found in the statements of Teglbjaerg, who on increasing the quantity of fluid ingested by 90 epileptic patients noted an increase in the number of attacks. McQuarrie and Peeler provoked the immediate appearance of attacks by giving abundant fluid combined with injections of solution of pituitary. Retention of water, more or less established by these researches, also has the effect of increasing the production and pressure of the cerebrospinal fluid.

The cerebrospinal fluid may aid in the production of epileptic paroxysms through modifications in its composition, its pressure or its distribution. As regards composition, numerous researches have led to purely negative conclusions. The fluid does not contain an abnormal amount of hypophyseal secretion or show special toxicity. The pressure of the fluid in persons with epilepsy has been found to vary at different times, apart from paroxysms. At the moment of attacks the

pressure is exceedingly high, which may contribute to the severity of the crisis. Physicians have tried to prevent attacks by changing the pressure of the fluid either by lumbar puncture or by the method of Weed and McKibben; the results are not encouraging. According to McQuarrie, Fay and Gamble, the favorable therapeutic effect of dehydration is due to reduction of volume in, and pressure of, the cerebrospinal fluid. Encephalograms have shown that in many patients there is partial dilatation of the subarachnoid space. A permanent lowering of the pressure has lessened or caused the disappearance of attacks. Efforts are now being made to modify the equilibrium of the fluid by operations on the sinuses.

As regards the relation of the endocrine glands to epilepsy, no one has established a definite rôle for any one gland. Anomalies of endocrine function and certain forms of opotherapy seem to play some rôle, but this rôle appears to be chiefly accessory. The suprarenal gland held attention for many years, but is today regarded as having no influence. Much stress has been placed on a hypophyseal pathogenesis of epilepsy. The secretion of the pituitary gland which is normally diverted into the cerebrospinal fluid, is said to be partially or totally lacking in persons with epilepsy (Altenburger and Stern), and this absence is said to play an important part in the pathogenesis of the disease. The arguments in favor of the view that the hypophysis is important were recently collected by Salmon, who recognized the existence of an epileptogenic sympathetic center in the diencephalic region and brilliantly defended this view.

The thyroid body cannot be looked on as a cause of epilepsy clinically, pathologically or experimentally. It should be mentioned, however, that a thyroid pathogenesis of epilepsy has been upheld by Bolten and Buscaino, who found octahedral crystals in the thyroid glands of persons with epilepsy, showing the formation of abnormal proteid substances. Injection of these crystals may cause the epileptic patient to regain consciousness. Epileptic attacks are influenced to some extent by ovarian activity, but the fact that the influence of the genital glands on epilepsy is peculiar to women shows that the true cause of epilepsy does not lie in an ovarian disturbance. All has certainly not been said on the influence of the parathyroid glands. Amelioration of epilepsy has been secured by grafting the parathyroid glands of sheep, but no special lesions of these glands have been found in epilepsy.

With due reserve concerning the possible rôle of the parathyroid glands, one may conclude that epilepsy is not a malady of the endocrine glands, though the functioning of these glands may influence in an accessory manner the evolution of the disease.

So far, anaphylaxis has not been found to be a fundamental cause of epilepsy. The epileptic attack cannot be identified with major anaphylactic shock or even with protein shock. Without doubt there are some elements of shock, but there are lacking the characteristic fall of blood pressure, marked leukopenia, disappearance of blood platelets and decided acidosis. Moreover, an essential symptom of epilepsy is loss of consciousness, which is lacking in major anaphylactic shock. Some epileptic paroxysms are preceded by phenomena analogous to hemoclastic crises, but no definite connection has been established. Cutaneous desensitization has been attempted as a therapeutic measure, but without marked results. Exceptionally, attacks may be provoked by the ingestion of certain foods (chocolate, beef, milk, eggs, cereals, cheese or kidney beans), and the intervals between attacks lengthened by their omission. Exceptionally, also, sudden explosive crises may be produced by protein shock, as after the injection of antityphoid vaccine or other serums. These occasional causes of epileptic crises, however, cannot be looked on as other than accessory, being complementary rather than truly pathogenic. The ancestors of some epileptic patients have presented manifestations of allergy, epilepsy and asthma are sometimes associated, and the possibility of anaphylactic phenomena of yet other origin may be surmised, but this seems hardly sufficient grounds for regarding epilepsy as an allergic disease.

In the experimental study of epilepsy, one may seek to reproduce only certain manifestations of the malady. The one which is provoked with the most success

is the epileptic crisis, which is not the most characteristic or the most pathognomonic. The most characteristic epileptic phenomenon is loss of consciousness, whether fugitive, as in absences, or occurring at the beginning or in the last phase of an attack. In certain cases of toxic epilepsy unconsciousness may be observed, with or without convulsive paroxysms. The appearance of unconsciousness, however, as yet is too difficult to establish and too much subject to error to be used as a major phenomenon in an experimental study of epilepsy.

The experimental study of epilepsy has not accomplished anything important in the last few years in the solution of the problem of pathogenesis. The majority of new facts have been derived from data concerning the production of convulsive crises by direct irritation of the brain, by vascular disturbances or by toxic action. The region of the brain that determines convulsions is still in doubt. The controversy concerning a cortical or a subcortical origin is still active.

To the toxins already known to produce seizures (absinth, picrotoxin, bromcamphor, cocaine and lactic acid) may be added the exceptional convulsant bulbocapnine; small doses of this substance cause sleep, moderate doses cause catalepsy and stronger doses may produce epilepsy; at times the symptoms may even recall the rigidity of decerebration. Insulin injected into rabbits and mice produces convulsions, which may be only a contingent sign of hypoglycemia; the importance of this, however, is that a glandular hormone may have a convulsant action. The occurrence of convulsions in human beings in the course of hypoglycemia has occasionally been reported, but research to determine whether "dysinsulinism" may enter into the pathogenesis of epilepsy has brought out nothing of value.

The greatest progress in experimental research seems to have been made by the method that combines a nerve lesion with toxic epilepsy. Claude and Lejonne, in 1910, showed that dogs, many months after the injection of a few drops of a solution of zinc chloride under the dura mater, present a special susceptibility to small doses of strychnine. Dandy and Elman performed analogous experiments by combining the production of various cerebral lesions with intoxication by absinth. After many weeks from one third to one seventh of the dose originally necessary proved sufficient to produce convulsions. The convulsant doses established for lesions of the rolandic zone are not the same as those for lesions of the occipital zone or of the cerebellum; following injury to the cerebellum large doses, approximating those that are required for normal animals, are necessary. Amantea produced convulsive phenomena by direct excitation of the cortex with strychnine. Clementi reported that small fragments of filter paper soaked in strychnine sulphate when applied to the cornua ammonis produce no direct reaction but create a state of special irritability of the nasal mucosa. If the animal is then made to breathe a strong odor, such as spirit of peppermint or ammonia, contractions of the nostrils are provoked, followed by localized epileptic movements which gradually become generalized and may border on a state of true epilepsy. These experiments show that lesions of the nerves lower the threshold for the development of convulsions. They produce epilepsy by a mechanism of summation analogous to that which occurs in men with head injuries who indulge in alcoholic drinks.

By biologic analysis of diverse fluids, efforts have been made to demonstrate a toxic mechanism which produces human essential epilepsy. The cerebrospinal fluid has been studied in vain, and urinary toxicity has not been proved to play a rôle. The experimental studies indicate the presence of toxic convulsant products in the blood of persons with epilepsy, but future research must establish the precise value of these indications. The toxicity is not caused by mineral or definite chemical constituents but is probably related to the albuminoid substances of the plasma. In spite of the vast amount of new data on experimental epilepsy, there is nothing to equal the results obtained by Brown-Séquard in his celebrated researches on guinea-pigs. He showed, moreover, that there may be epilepsy of purely nervous origin, independent of humoral phenomena.

New data as to the pathologic physiology and the pathogenesis of epilepsy may be summed up as follows: The vascular substratum of epileptic crises is

now established. The epileptic person presents remarkable organic instability not only in the reactions of the sympathetic nervous system but in the nitrogen equilibrium, blood sugar, hydrogen ion concentration of the blood, leukocytic formula, equilibrium of blood pressure, cerebrospinal fluid pressure, etc. With such instability, the attacks are favored by certain humoral modifications and more or less prevented by others. The crises are influenced in their appearance or disappearance by the functioning of the endocrine glands. However, the new data, important though they are, concern only accessory conditions which change the irritability of nerve tissue. The abode of the enigma and the primary cause are still unknown, as is also the condition which determines the instability which breaks forth, in the manner of a shock, into the vasomotor crisis, the substratum of the attacks. One must seek to discover this condition by a more intense study of pathologic physiology and by a constantly closer approach to the experimental production of epilepsy.

Tomorrow may bring the key word to the enigma, but there is slight probability that it will cause epilepsy to cease to be a disease of double aspect, neurologic and humoral, which in this respect is perhaps unique in pathology.

RECENT ADVANCES IN THE KNOWLEDGE OF THE SYMPTOMATOLOGY AND DIAGNOSIS OF EPILEPSY. O. CROUZON.

The temperature of a patient may rise as much as 1 C. (1.8 F.) after an attack of epilepsy, but only in status epilepticus is true hyperthermia observed.

The diastolic pressure in most persons with epilepsy is normal, but the systolic pressure is not governed by any rules. The pressure and amplitude of oscillations of the pulse vary with each patient, many showing an increase during and after attacks, which permit the supposition that the modifications of arterial pressure are determined by the attacks and therefore play no important rôle in their pathogenesis.

Study of the blood reveals that after attacks there is a diminution in the number of red corpuscles, but an even more marked increase in the number of white corpuscles; there is also a decrease in hemoglobin, with less reduction in the quantity of oxyhemoglobin, and the coagulation time is shortened. The epileptic crisis is accompanied, moreover, by abundant hyperleukocytosis, the cells being chiefly lymphocytes and large mononuclears. The first phase, vascular or sympathetic, shows leukopenia in the capillaries as a result of spasmodic vasoconstriction. In the second, parasympathetic phase, there are vasodilatation, leukocytosis and colloidoclasia of the tissues.

Do epileptic attacks disturb the labyrinthine reactions? Temporary impairment of labyrinthine activity usually follows generalized convulsive crises. Persons with epilepsy suffering from vertigo present persistent instability of vestibular reactions. In periods of calm, the reflex activity may remain at a relatively fixed low threshold of excitability. May excitations of vestibular origin break forth into epileptic phenomena? This has been observed in only about one fourth of the cases, yet it shows that the cortex is perhaps not the only point of origin of epileptic outbreaks.

The oculocardiac reflex is considerably exaggerated in epilepsy. Patients having the smallest number of attacks show the least exaggeration of the reflex, and vice versa. Treatment with bromides diminishes the exaggeration of this reflex. The reflex is least exaggerated after a crisis. Injection of 2 mg. of atropine abolishes the exaggeration in about an hour. Some authors have found a residual tachycardia in 62.5 per cent of patients after the cessation of ocular compression, and they attached great diagnostic value to this sign, looking on it as a sort of sympathetic epilepsy. Tests with pilocarpine and epinephrine have given the following results: injection of pilocarpine hydrochloride produced a varied effect; in seven instances it clearly augmented the intensity of the reflex a half hour after injection. Epinephrine increased the oculocardiac reflex five minutes after injection.

The carotid sinus, the small dilatation at the level of the bifurcation of the carotid arteries, is of great importance in a whole series of reflexes. It has been found that the reflexes of the carotid sinus are diminished in epilepsy. As a result, the vasomotor reflexes and the arterial pressure in epileptic persons present great instability. Compression of the carotid sinus may in certain cases of epilepsy give rise to typical convulsive attacks.

Marchand, Picard and Courtois, in 1931, studied seventy-five cases of idiopathic epilepsy and found an increase in the spinal fluid pressure in 13.5 per cent, slight albuminosis in 22 per cent, a positive reaction to Pandy's test in 17 per cent, the Weichbrodt reaction in 4.5 per cent, slight lymphocytosis in 13 per cent and a positive Wassermann reaction in three cases. The benzoin test showed no precipitation in the first five tubes (syphilitic zone) in any case but precipitation in the first tubes of the meningitic zone in three cases.

De Thurzo, studying the biologic and serologic methods for the diagnosis of epilepsy, said that while there are no gross anomalies, the colloidal reactions are frequently modified. He stated that the reaction to india ink is frequently positive.

Di Renzo, in 1930, estimated that the convulsive crisis coincides with the irruption of acids into the circulation, an irruption which lowers the alkaline level of the blood and augments the quantity of calcium ions in the plasma.

There may be abortive and incomplete manifestations of epilepsy. Vertigo may for a long time be the only manifestation. It is the most striking symptom of an incomplete motor syndrome, other manifestations of which are jerks limited to some member (sometimes the lips or jaws), apoplectiform attacks and myoclonia. The myoclonia may be fibrillary or paroxysmal, the latter being called "petit mal moteur." True epileptic myoclonia or Unverricht's disease, is a distinct type. There is also an intermittent type in which momentary shocks may precede the appearance of attacks by many years and evolve to a continual type analogous to Unverricht's disease.

Kojewnikov's syndrome consists of cortical epilepsy, abortive or accompanied by loss of consciousness, and of clonic shocks occurring uninterruptedly in the intervals between attacks and striking certain regions. Souques has seen the convulsive attacks disappear under the influence of phenobarbital, but the jerks continued. He thought that these may arise from a central lesion (an extended lesion reaching to the cortex of the central region). The polyclonia of Unverricht resembles common epilepsy; the polyclonia of Kojewnikov, jacksonian epilepsy.

Traumatic epilepsy may present diverse localized forms, varying from the purely motor, without loss of consciousness, sometimes secondarily generalized, to forms with tonic predominance, athetotic states and forms characterized by crises of flaccid paresis with vasomotor phenomena. Villaret saw no cause for distinguishing localized forms of traumatic epilepsy from generalized forms; in the latter there are always localized predominantly motor disturbances, clonic, in the rolandic cortex, which are followed by secondary diffusion.

Ramsay Hunt described in some cases attacks characterized by a sudden cessation of postural function with transitory loss of consciousness. He thought that they were static attacks as opposed to convulsive or kinetic seizures. In epilepsy a release of the kinetic mechanism produces convulsive manifestations, while a liberation of static mechanism is characterized by loss of posture control. All agree that these cases represent a dissociation of cortical functions with functional liberation in limited cerebral territories. In the myoclonic cerebellar synergy described by Ramsay Hunt static attacks are observed. There are a certain number of convulsive crises the peculiarities of which differentiate them from classic epileptic attacks and permit the thought of different, perhaps corticopyramidal, lesions. One may mention the tonic manifestations described by Jackson, cataplexy, narcolepsy and pyknolepsy. Tonic tetanoid crises have been observed in the course of neuromyelitis optica; the lesions found at autopsy included among others a peduncular lesion adjacent to the locus niger. These crises belong to the group of subcortical epileptic manifestations. Cataplexy consists in a sudden and

brief loss of postural tonus without loss of consciousness. Pyknolepsy consists in frequent attacks with slight inhibition of psychic functions, trembling of the legs, winking of the eyelids, etc. These crises may cease spontaneously or may be replaced by epileptic attacks.

Marchand and Courtois classified extrapyramidal epileptic phenomena in three groups: (1) more or less localized phenomena, the subject remaining conscious; (2) generalized motor phenomena, possibly with clouding or loss of consciousness, rigidity, tonic attacks, etc. and (3) attacks approaching classic epilepsy.

According to Cruchet, spasmodic torticollis may be encountered with epilepsy in three forms: (1) as a localized symptom of epileptic attacks; (2) as an epileptic equivalent; (3) in association with epilepsy without any causal relationship. Since 1900, an organic origin of spasmodic torticollis has been accepted, lesions of the midbrain being especially incriminated. Pierre Marie and Léri drew attention to the existence of osteo-articular lesions of the cervical vertebral column caused by irritation of the fifth and sixth cervical nerves and reflex excitation of the spinal nerves. The important report of Barré brought this question into prominence. Marchand and Bauer thought that their observations support the mesencephalic theory of spasmodic torticollis. M. Cornil reported that, aside from the spasmodic torticollis of petit mal type observed by different authors, there exists a spasmodic torticollis of mental type, which does not appear to be an epileptic equivalent. It comes on periodically and resembles the manifestations of essential epilepsy.

Sterling reported a case in which sudden sharp paralysis was followed by an epileptic attack, after which normal motility immediately reappeared; later the paralysis reappeared and was followed by convulsive attacks and then by movements. This indicates that a positive stimulus provokes convulsions and a negative stimulus provokes paralysis.

Claude and Baruk studied cases of epilepsy which seemed to show a regressive stage under the influence of treatment; they called these manifestations "degraded forms;" in conclusion they presented the following practical idea: Every time a physician sees mental disorders caused by phenobarbital, he should ask himself if he has not observed the transformation of motor disturbances into confusions and interpret the reaction not as intolerance for phenobarbital but as a regression of symptoms. In such cases he should increase the dose of phenobarbital progressively instead of discontinuing the administration of the drug.

Should interrupted visceral or sensory manifestations be accepted as epileptic equivalents or aftermaths? A certain number of sensory, visceral and psychic syndromes because of their coexistence with epilepsy in the same person or in the same family, their essential paroxysmal course and the exhaustion that they leave behind them should be called latent or abortive epilepsy. Among the visceral paroxysms there have been reported angina, asthma alternating with epilepsy and thymic asthma with spasm of the glottis. The resemblance of all these to epilepsy is debatable, yet many agree with Féré that internal convulsions are only the first manifestation in a convulsive course. Gastric disorders are classed as latent epilepsy because of their paroxysmal character. Tic douloureux of the face and epileptiform neuralgia also belong here. Baruk reported a case in which the epileptic crises were replaced by a brutal constriction of the throat and another case in which the crises were characterized by a sudden sensation of pressure in the occipital region, descending to the vertebral column and followed by erection and ejaculation. The patient had been overcome in the preceding year by a sudden loss of consciousness with a fall preceded by an erection. It is expedient, as Baruk said, to be circumspect in the diagnosis of visceral crises, above all of isolated visceral crises. It is important to distinguish these crises from those occurring in the neurotic or psychotic person, which are less brutal and briefer and disappear at the will of the patient. The existence of these visceral crises is explained by the importance of the organovegetative centers in the brain.

The equivalents, or sensory paroxysms, are numerous; many of them include temporary blindness, suggesting symptomatic amaurosis of migraine, as they bear evidence of a spasm of the central artery of the retina. Viallefont and Maillot observed the association of hemeralopia and hereditary epilepsy. Among the sensory paroxysms, one may cite diverse illusions or hallucinations arising independently of convulsive or vertiginous attacks. The common characters of these hallucinations are the suddenness of their appearance and disappearance and their brevity. All these sensations may play a rôle in the production of delirium and may form the point of departure for impulsive behavior. Finally, anosmia is a frequent symptom of epilepsy; it may be transmitted and affect many generations.

CONDITIONS RELATED TO EPILEPSY

In addition to the visceral or sensory symptoms the paroxysmal character of which permits one to consider them equivalent, there are certain other diseases that approach epilepsy, either in their paroxysmal character or in nature of the motor disturbances. These are migraine, asthma, urticaria, Raynaud's syndrome, certain cardiac disorders, spasmophilia, etc. Some authors have reported asthma replacing the epileptic crisis or alternating with it. Urticaria has been observed as a premonitory or an alternate manifestation. Others have suggested that certain syncopal forms caused by a circulatory disturbance and characterized by a total and instantaneous loss of consciousness should be considered as close relatives. Raynaud's syndrome has been thought to be an alternate of epilepsy; angina pectoris and tic douloureux have also been considered related. Pagniez sees no connection between the tetany of adults and epilepsy, but he thinks the relation more complex between spasmophilia of children and epilepsy, as research shows the presence of humoral modifications similar to those in evidence in the blood of persons with epilepsy near the time of the crises.

Most attention has, however, been given to migraine. The relation of migraine and epilepsy was studied by Louis Jean. Piorry was the first to employ the term "migraine accompagnée" to designate the nervous disturbances associated with certain attacks. Trousseau did not consider epileptiform neuralgia identical with epilepsy, but stated that while they might be merely coincidental the two diseases could be due to the same cause.

Lasègue, Bouchard and others have stated that there is no relationship between migraine and epilepsy. Sordat found few cases of migraine in persons with epilepsy, but estimated, with Charcot and Féré, that ophthalmic migraine is not without a close analogy to epilepsy. Féré stated that among the phenomena which may accompany ophthalmic migraine he would include epilepsy, especially partial epilepsy, whether it appears previous to the migraine or follows it or the two syndromes appear at the same time.

It may be true that there is a parallelism between migraine and epilepsy. However, as Schule said, sharp psychic disorders the symptoms of which definitely resemble epileptic and hystero-epileptic states may be seen in patients with migraine without the least justification for considering the condition truly epileptic.

Pierce Clark cited a case in which migraine served as the aura of epilepsy. In certain cases there may be an attack of epilepsy following an attack of migraine, which is then referred to as migrainous epilepsy. Cornu admitted that attacks of migraine may cause convulsive states similar to, and sometimes mistaken for, the great crises of epilepsy, sometimes followed as in true epilepsy by partial paralysis due to inhibition. Gordon, who studied the relation of the two diseases without admitting their identity, thought that they may be different functional effects of the same cause.

Pasteur Vallery-Radot summed up the arguments in favor of the relationship of the two diseases: (1) In migraine, auras comparable to epileptic ones are found; (2) the same causes may produce attacks of migraine and of epilepsy, particularly ovarian, endocrine and digestive disturbances, while allergic reactions may take one form at one time and the other form at another; (3) in the course of the epileptic crisis there is anemia in the brain owing to vascular spasm, which

resembles the pathologic process of migraine; (4) humoral researches show that certain epileptic crises, as well as certain attacks of migraine, may be preceded by colloidoclastic shock, by vasotrophic shock, by a notable augmentation of the alkalinity of the blood, by diminution of calcium, etc.; (5) the administration of bromides and phenobarbital and the production of protein shock have given good results in migraine as well as in epilepsy. [So also have dehydration, starvation and the ketogenic diet. W. F.]

Pagniez does not agree with the opinion of Vallery-Radot but claims that the relation of true migraine to epilepsy is confirmed by indisputable facts and impressions. He states that among the diseases presenting crises there is a first group which comprises asthma, urticaria, spasmodic coryza, hay fever and Quincke's disease, which are all chiefly allergic diseases involving the skin or the mucous membrane of the respiratory tract. In a second group he places migraine and other nervous and gastro-intestinal manifestations. These two groups may have some relation to the famous gouty dyscrasia. Epilepsy is more closely connected with the second group than with the first. It also resembles another group, which comprises the paroxysmal psychoses. Finally, it shows some resemblances to the group that includes tetanus and spasmophilia.

DIAGNOSIS OF EPILEPSY

According to Jean Picard, one should not base a diagnosis simply on the duration of the aura, since this may normally be prolonged and be accompanied by hysteriform symptoms. Various manifestations of hysterical aspect may be of epileptic origin, such as epileptic somnambulism, motor disorders of varying degrees and the tics. Different methods have been proposed to establish a differential diagnosis between epilepsy and simulation or hysteria, but no laboratory test has proved as adequate as clinical examination.

EVOLUTION OF EPILEPSY

Essential epilepsy, which most frequently is caused by an inflammation of the brain in infancy, appears after a latent period under various forms. Pierce Clark upheld the idea that grand mal appears many years after petit mal or minor disturbances of an epileptic nature. Certain patients have but one attack during life; others have two or three a week; still others have several every day. Irregular cycles are sometimes in evidence.

There are somtimes recrudescences of paroxysms from unknown causes (which are repeated in series the same day or the same night), accompanied by an elevation of temperature and followed by a prolonged general depression. Such series may be observed with all forms of paroxysms (e. g., vertigo, or shock). When the series presents a graver aspect, it is called status epilepticus.

According to Hartenberg, an epileptic habit exists, a tendency to the reproduction of paroxysms, which is the third pathogenic factor in epilepsy. While the early attacks may be widely spaced, the later ones may occur frequently without any apparent provoking cause. This epileptic habit may be explained by several hypotheses: by the persistence after the crises of microscopic alterations in the brain, augmenting irritability; by sensitization of the nervous system by toxic or humoral influences, and by the opening of nerve paths through which the initial irritation propagates itself with growing facility. The idea of these phenomena is important from a prognostic point of view. It is more difficult to cure a subject who has had a greater number of attacks; hence the necessity of treating the patient as early as possible, before the habit becomes confirmed, and the equal necessity, because of the latent persistence of the habit in the brain, of maintaining the patient in hygienic conditions and continuing to treat him for some time after the cessation of the attacks.

There is a popular notion that the emotions play a rôle in the production or recrudescence of epileptic attacks, but according to Vallon, the emotions cause outbursts of epilepsy only in susceptible subjects.

Certain occupations that lead to an increased flow of blood to the brain or those that require the use of toxic substances are detrimental. Poor hygiene, continued sitting up at night, fatigue, a faulty diet and excessive use of alcohol are predisposing causes. Various medicines, such as strychnine, cocaine, opium, ether, nicotine and quinine, have a provoking action, as do also electric treatments and rotatory movements. Sainton reported crises following enemas. Certain foods, peculiar to each patient, may bring on a crisis. The abuse of sexual pleasures and onanism seem to favor the appearance of attacks; more rarely, absolute continence increases their frequency. Congestion of the head, changes in body temperature and infections generally have a predisposing influence.

Attacks of epilepsy often cease to occur for a more or less prolonged time when the patient is attacked by an intercurrent febrile condition. Numerous physicians have reported that intermittent fever arrested attacks of epilepsy; pneumonia, rheumatic fever, erysipelas, a fracture, scarlatina, pleurisy, anthrax and vaccination have produced analogous results. Lannois said that certain infections (erysipelas and pneumonia) have a favorable influence on epilepsy and that others (typhoid) act unfavorably. The effect of grip seems to vary. Sometimes it shows a favorable influence, without, however, causing complete cessation of attacks, but it may also invoke disastrous complications; most frequently there is no appreciable effect. It may precipitate mental disturbances.

Cosmic influences, such as the weather, barometric pressure and lunar cycles, have been considered to influence the appearance of attacks.

Féré estimated that the frequency of attacks is greatest at about 8 p. m. and 4 a. m. According to the researches of Toulouse and Piéron, the occurrence of seizures depends not on the time of the day or of the night but on the state of waking or slumber; there exist two maxima of frequency, one after lying down and the other at the moment of awakening. In studying the appearance of crises according to the days of the month, Toulouse and Piéron observed a certain periodicity of attacks of from eight to ten days. The attacks were more frequent in May and October. According to the researches of these men and of Marchand, the frequency of attacks seems to diminish with the rise of outdoor temperature.

The influence of menstruation (puberty and the menopause) appears incontestable. There are cases in which the epileptic attacks occur synchronously with the menstrual periods, i. e., menstrual epilepsy. In one category, the menstrual periods and the crises coexist. In another, the monthly periods are replaced by seizures. Souques reported many cases in which puberty, pregnancy, the menopause and ovariectomy had a favorable influence in diminishing the frequency of crises. It is probable that the secretion of the ovaries has an influence, and if abnormal menstruation may influence epilepsy, it is difficult to explain how normal menstruation modifies it either by irritability of the nerve centers or by modification of the body fluids. How can one explain menstrual epilepsy? The first impulse in the menstrual cycle is located in the anterior lobe of the hypophysis, the secretion of which excites the internal ovarian secretion. Menstrual epilepsy may be explained by reflex disturbances spreading from the genital organs or by humoral imbalances of which the origin and nature have been sought in disturbances of the thyroid and parathyroid glands. Souques said that though the explanations made are not sufficient, clinical observations of menstrual epilepsy exist which establish the reality of a rare variety of epilepsy in close relation with menstruation and the great moments of genital life.

Monosymptomatic epilepsy is rare. Delavalette reported the case of a man who for seventeen years had only petit mal attacks but showed deterioration which may have been a form of epileptic dementia. In most cases epilepsy ceases after a relatively short time to be monosymptomatic, and in addition to the epileptic equivalent symptom a typical general attack appears after a few months.

Recovery in cases of infantile epilepsy has been reported, but most frequently such cases are instances of infantile convulsions rather than true epilepsy. However, according to several authors, recovery may take place at a more advanced

age. (This does not, of course, include symptomatic epilepsy, which is naturally susceptible to cure by treatment of the cause.)

How long after the disappearance of crises should antiepileptic treatment be continued? Legrand du Saule said that after two or three years of freedom from attacks the amount of bromide may gradually be diminished. Féré and others believed that the administration of bromide should not be stopped for ten years after the disappearance of the attacks.

STATUS EPILEPTICUS

In status epilepticus the temperature may be moderate at the beginning, but it rises to 40 C. (104 F.) or higher in the terminal period. The temperature is of great importance in prognosis. If it rises gradually, the condition is less grave than when it suddenly rises to a high point. Bouttier considered that generally there is arterial hypotension; the oscillometric amplitude is considerable immediately after the convulsive crisis but diminishes later. The rhythm of the pulse is modified in the course of attacks and may rise to 130 at the moment of the crisis. The oculocardiac reflex appears marked to some authors. The respiratory rhythm may become irregular without, however, being of the Cheyne-Stokes type. The cerebrospinal fluid rarely shows alterations. The amount of albumin varies considerably. When the status is symptomatic of a diffuse involvement of the nerve centers, the amount of albumin may be increased. This may reveal cerebral syphilis. Several authors have found an increased amount of nitrogen in the blood preceding the epileptic crises, and others think that retention of urea may be an element in the differential diagnosis of epilepsy and hysteria. A varying degree of leukocytosis, as well as an increased fragility of the erythrocytes, has been noted. Damaye expressed the belief that status epilepticus is accompanied by eosinophilia when recovery is at hand. In fatal cases, there are polynucleosis, a decrease of lymphocytes and absence of eosinophils.

The pilomotor reflex is always lively. The injection of pilocarpine hydrochloride has a marked action on sweating. The pupils are wide, and the pulse is forceful.

Psychic Epilepsy. Jean Abadie.

That there is no epilepsy without mental disturbance, whether slight or grave, is now accepted by all students, but this was not recognized until 1860. Mentality in its quantitative aspects does not enter into the essential composition of the epileptic character. Epilepsy may be encountered with all degrees of intelligence. Numerous examples of men of talent and genius who were incontestably afflicted with epilepsy have been reported in history. A large number of persons with epilepsy acquire a psychic development that is normal for all purposes and maintain proper intellectual function. However, the lesions of the nerve centers, congenital or acquired, susceptible of provoking epilepsy are capable of causing a disturbance of the mental and emotional growth. All states of mental deficiency may be observed in epilepsy, from idiocy up to the slightest mental impairment. In all these cases it is a question not of a consequence of epilepsy but of the association of two cerebral syndromes originating from the same organic cause.

Mentality in its qualitative aspect, on the contrary, is of importance, in that there is frequently a special form of psychic activity of which slowness is the dominant factor. To distinguish this from other forms of mental sluggishness Ducosté gave it the name "comitial bradypsychia." The psychic slowness in epilepsy is habitual, permanent and independent of paroxysmal attacks; it may even exist without any quantitative alteration in the mental base. It is, however, a gross error to think that all persons with epilepsy are and remain bradypsychic; numerous examples demonstrate that certain ones may have a different type of mental activity, even completely the opposite.

The epileptic character, reduced to its fundamental psychopathologic expression, shows the following essential traits: It is built on a basis of affective depression, which renders the person habitually somber or sad, indifferent or even apathetic; on this foundation appears an extreme variability of mood, with sudden changes

without motive or for futile reasons, expressing themselves by a temporary exaggeration of the depression to a feeling of inferiority or pessimism or by the transitory appearance of feelings of unreasonable personal aggrandizement and egotistic exaltation. Finally, what gives the epileptic character its particular aspect is a dissimulated irritability, which is always present and under stress may burst out suddenly. This also manifests itself by excessive suspiciousness, with belief in the hostility of the ontourage and ardent or spiteful recriminations; sometimes it shows itself in passionate reactions and even in acts of impulsive violence.

This triple association of habitual apathy with brusk mobility of mood and paroxysmal irritability constitutes the character of the epileptic person, who thus appears inert but easily inflammable and often explosive. Showing himself under very different aspects following momentary impulses, sometimes apparently inoffensive, crafty and obsequious, sometimes quarrelsome, undisciplined and aggressive, he is always badly adapted to his surroundings. Some authors have added other traits. It appears clear, however, that these constitutional disturbances of character should be attributed chiefly to the association of epilepsy with different forms of superadded psychic disequilibrium, an association the more frequent because the two manifestations may have their origin in the same organic lesions of the nerve centers. The epileptic character may appear and persist even in the absence of convulsive attacks. Its recognition in infants is therefore of great importance. It may accompany delayed epilepsy, adding itself to the former character and even at times transforming it. In a case of latent epilepsy its discovery may establish the diagnosis.

Three kinds of psychic disorders of epilepsy may be distinguished: those which precede the convulsions, those which accompany them and those which follow them. The preconvulsive psychic disorders comprise the psychic prodromes and auras. The former may appear alone or may be associated with other prodromal manifestations of a different order; they develop a few hours or days before the attack and consist in a manifest change in the habitual mental attitude, which recurs repeatedly in the same subject with the identical disturbances of emotion, of thought or of action. The psychic auras are psychosensorial, emotional, ideative, or psychomotor; they may exist alone, in combination with each other or in association with stereotyped motor, sensory or visceral auras. They announce the imminence of the crisis.

The paraconvulsive psychic disturbances, those that are manifest during convulsive attacks, consist essentially in sudden and complete loss of consciousness preceding the convulsion, the evolution of which constitutes the period of epileptic coma. This early and prolonged deprivation of consciousness is the essential psychic phenomenon of the epileptic convulsive crisis. It is also the pathognomonic symptom of the epileptic attack. In Bravais-Jacksonian epilepsy, the loss of consciousness may occur only when the convulsions reach the face or become general. When that happens, however, the loss of consciousness is so rapid that it seems at times to precede the convulsion, and in that case the differential diagnosis between the two epileptic syndromes is particularly difficult.

Postconvulsive psychic disorders are never absent. In the period of cerebral exhaustion which follows the convulsion modifications of the mental state, more or less prolonged and intense, always appear. The stertor, the profound sleep and the cerebral torpor which follows the awakening are the simplest manifestations. Complete amnesia for the events of the crisis constitutes another phenomenon which is of as great importance as the complete loss of consciousness preceding the crisis. Postconvulsive mental confusion occurs with great frequency in the accentuated forms of epilepsy. This confusion may assume all forms, from the light form of the twilight state, with more or less coordinated and tranquil automatism, to severe forms with stupidity and more frequently great agitation, extreme violence of reaction and disorders and especially dangerous activity. It is here that most of the activities described as epileptic mania, or furor, should be placed; they only dimly resemble true mania and are allied to mental confusion by the dulness and disorientation which always accompany them. These confusional mani-

festations may also appear, although less often, as diverse forms of amnesia. There may be observed also simple disturbances of character analogous to the psychic prodromes, but with a more marked tendency to symptoms of depression and quarreling. The duration of postconvulsive psychic disorders is extremely variable, depending on their intensity and clinical forms.

The clinical existence of psychic epilepsy is no longer doubted. It may exist alone or in association with convulsive attacks, and it includes all the epileptic impulsions and psychoses, to which it seems logical to add absences, attacks of vertigo, certain disorders of sleep and the static attacks of Ramsay Hunt, accompanied by more or less complete loss of consciousness. The pyknoleptic attacks described by Feldmann as short narcoleptic attacks are today considered epileptic absences, mild, of short duration, of daily repetition and with a tendency to spontaneous recovery. The epileptic disturbances of sleep consist in habitual and paroxysmal motor agitation during sleep, brisk awakenings, frequent dreams of painful character and real nightmares. Closely connected with these disturbances of sleep in epilepsy are the attacks of narcolepsy and simple soporific attacks; Crouzon reported an instance of a true soporous state.

Epileptic compulsions may develop before the attacks as prodromes or auras, may appear chiefly as postconvulsive confusional states or may exist independent of the paroxysms and thus assume the character of true psychic equivalents. Of all these epileptic compulsions, the most frequent appear to be those tending to homicide. A murder done by an epileptic patient possesses characteristics such that its morbid nature is often recognized at once. The suddenness, the absence of premeditation and precaution, the lack of interest and of profit and, above all, the indications of brutal violence, blind savagery and complete amnesia all point to an origin in epilepsy. Less frequent in psychic epilepsy are the equivalents compulsive to robbery, incendiarism, destruction, suicide, self-mutilation and attempts at rape. These impulsive manifestations more often occur in the course of furious confusional states with agitation.

In addition to the various demonstrations of procursive epilepsy, Charcot has described in detail the coordinated, though unconscious, activity which he designated "ambulatory automatism." Pitres afterward insisted on qualifying the description by calling the condition "impulsive vagabondage." Several recent works have emphasized the complexity but logical appearance and eupraxic execution of these impulsive acts.

Of all these isolated epileptic compulsions it may be said that the impulsive act is essentially characterized by the following qualities: suddenness, independence of external conditions, automatic accomplishment, ordinarily brusk execution, short duration and intermittent and even periodic reiteration. Two other traits imprint themselves on this cachet of epilepsy, unconsciousness during the execution of the act and complete amnesia following it. In spite of these criteria and the recent works on the subject, the interpretation of automatic acts of an epileptic nature remains sub judice.

The psychoses of epilepsy are less definitely demonstrable clinically, and the divergent opinions of authorities do not permit describing these manifestations as a whole. In the opinion of certain writers, epileptic psychoses, or attacks consisting of true psychic equivalents, do not exist; they always look for confused states before or after convulsions. Others, on the contrary, look on all transitory deliriums developing in identical and periodic attacks, with a sudden outbreak, a short duration and a sudden blunt termination, as epileptic psychoses. The dominant symptom is agitation of manic type, reaching furor with violent and dangerous impulses and producing a state typical of Falret's intellectual grand mal. Some consider that the fundamental symptoms are confusion, hallucinations, dreaming or stupidity. Others have stated that there are forms with excitation and depression and mixed states without other particular semeiologic characters. It has even been proposed to regard as epileptic the various forms of periodic psychoses, intermittent or cyclic, or at least to establish between the two conditions close bonds of relationship. Krisch even asked, in 1922, if he could not connect

all the manifestations of the manic-depressive psychoses with epilepsy. There are certain prolonged, even chronic, psychoses in the same category as epilepsy which manifest themselves as maniacal states with peculiar characters of violence and impulsiveness, as melancholic states with reactions of blind anxiety, as systematized delusions of persecution with criminal compulsions, as hypochondria with a tendency to self-mutilation or as visual hallucinations of mysticism and ideas of grandeur. Boven published, in 1920, a general study on the religious delusions of persons with epilepsy. An attempt has been made to determine the association of epilepsy with various psychoses, such as toxic psychoses, in particular those of alcoholism. Finally, there should be mentioned in connection with epileptic psychoses the delirious states of convulsive epilepsy, in which under the influence of treatment the great convulsive crises are replaced by intermittent delirium, ordinarily grave and with violent and aggressive reactions.

The diagnosis of epileptic psychoses, and in a more general fashion of latent psychic epilepsy, thus appears as a problem the solution of which is sometimes impossible on clinical examination, though this is frequently indispensable both from a medicolegal and from a therapeutic point of view.

In former times, dementia was considered the common if not the universal result of epilepsy, and in particular as the banal termination of epileptic psychoses. Epileptic dementia was believed to be the result of cerebral exhaustion, provoked by the early development, the persistence and, above all, the repetition of attacks. It has been described thus: a slow but progressive course proceeding by exacerbations developing parallel with the number and the repetition of attacks, remitting during their arrest and beginning again with each recurrence, increasing more than ever after serial attacks and terminating after a struggle of many years in torpor and marasmus. A more rapid advance may be recognized in youth and old age than in adult life.

More recent work has demonstrated that the dementia associated with epilepsy is by no means always identical; the forms presented are, on the contrary, so different from one another that they defy unitary description. An epileptic dementia does not exist, but epileptic patients may show demented states, the clinical manifestations of which singularly resemble other forms of dementia. Several authors have stated that in youth epilepsy is complicated by dementia chiefly at the onset of puberty or at the end of adolescence; that in adult life the beginning of sexual involution is a dangerous period and that the aged person with epilepsy tends most frequently to undergo mental decay. It has also been confirmed that dementia almost always occurs in infantile encephalopathies, in cases of acquired and persistent cerebromeningeal lesions in adults and in cases of diffuse or circumscribed cerebral insults in aged persons. In infancy, the dementia may assume the form described by J. Voisi under the name "pareto-spasmodic epileptic dementia," which indicates clearly the causative influence of permanent organic lesions. During adolescence, epileptic dementia evolves under an aspect comparable to that of dementia praecox in its many varieties. In the adult it may be expressed as simple dementia, sometimes delusional, or as paralytic dementia with association of physical symptoms, so that the differential diagnosis from dementia paralytica is at times rendered difficult. In the aged, the dementia assumes characters so similar to those of senile dementia that one might speak less of epileptic dementia than of senile dementia with epilepsy. According to this, a great many of the phenomena accepted until now as demonstrative, may be eliminated from the picture of epileptic dementia and considered simply as various banal forms of dementia associated with an epileptic syndrome. According to others, the designation should be reserved for the slow dementia that may be observed in all epileptic persons, young or old, which appears as simple chronic intellectual obtundity. Thus the conception of epileptic dementia, after remaining for so long a fixed pathologic notion, has become again a question which calls for new clinicopathologic study.

Unconsciousness during the paroxysms and amnesia afterward are the two fundamental rules of common epilepsy, but these rules are not absolute; the

existence of epileptic attacks with more or less complete conservation of consciousness and memory is admitted today without discussion. It has been demonstrated that all epileptic phenomena, from the prodromes and the auras to the great convulsive attack, the most diverse equivalents and the most varied manifestations of psychic epilepsy, may take place during consciousness and be fully remembered. Epileptic absences also may appear with conservation of consciousness and memory. In certain absences complicated by automatic acts the subject may or may not speak and act, correctly or not, with consciousness of what he says and does but without the influence of his true personality, as though the acts were committed by a different person. Aphasic or anarthric attacks with preservation of consciousness have been observed as a special form of epileptic absence. Bèhague showed the existence of similar attacks taking the form of dysarthria or of anarthria in cases of frontotemporal lesions and of Wernicke's aphasia or of dysphasia in cases of temporo-occipital lesions. In a case observed by Martimor, memory for absences lasted about an hour; after that it was lost, under the form of retarded amnesia. In this group of phenomena should be ranged those described by Claude and Baruk under the designation of degraded forms of epilepsy. These authors claimed that under the influence of treatment by phenobarbital in increasing doses, true epileptic automatism was transformed into psychologic or psychomotive automatism. In the static crises of Ramsay Hunt the loss of consciousness may be incomplete or may not exist. In pyknoleptic attacks, the interruption of consciousness is often so brief and incomplete that the young subjects do not lose the thread of events surrounding them. Cataleptic attacks are placed by many among the abortive forms of epilepsy with conservation of consciousness. The generalized convulsive attacks, of which it has been said with reason that the complete loss of consciousness and consecutive total amnesia are the fundamental psychic symptoms, may also be accompanied by more or less entire conservation of consciousness and memory.

Though the number of similar observations is numerous and varied, the notion of a possible conservation of consciousness and memory in the great convulsive epileptic attacks is not accepted by all authors, even with reserve for the rarity of such a phenomenon. Certain workers consider cases in which the patient is conscious as instances of Bravais-Jacksonian epilepsy with generalized secondary convulsions. Others consider that there is an association of epilepsy and hysteria, the amnesic attacks being epileptic and those with preservation of memory hysterical. Some think that a loss of consciousness exists but that it is so brief that it passes unperceived by the subject and by those about him. Others regard such cases as instances of epilepsy attenuated by treatment in which the convulsive attacks tend to become more or less conscious.

Status epilepticus may exist with conservation of consciousness, but on this point little is known. Marchand and Olivier, in 1906, reported the case of an epileptic patient who for nine hours presented a convulsive state with forty-five attacks occurring in series of five or six, and a temperature of 39 C. (102.2 F.); she was able to talk during the entire course of the convulsions. Souques and de Massary, in 1924, reported the case of a man with traumatic epilepsy whose attacks were of the jacksonian type, reaching the face and lasting one or two minutes each, four or five hundred occurring in twenty-four hours, with no loss of consciousness.

The epileptic impulsions may also escape at times the rule of unconsciousness and amnesia; latent psychic epilepsy may do the same. Impulsions to acts of violence and murder with more or less complete conservation of lucidity and memory have been reported. Layen, in 1870, recognized the epileptic nature of a double parricide which was committed in a state of consciousness and of which the murderer had retained in memory the finest details. Tamburini reported impulses to acts of destruction and homicide in persons with epilepsy who reported the reprehensible character and at the same time the irresistibility of their acts. Roncoroni, in 1904, published the history of a murder committed by an epileptic person with retarded amnesia. Schlub, in 1907, reported an impulsive homicide

which he attributed to latent epilepsy. Trénel and Raynier, in 1913, described an impulsion to homicide while the subject was in a twilight state, during which he experienced the conscious representation of a murder which he felt impelled to carry out. The epileptic impulsions to suicide in their conscious mnemic form were the object, in 1899, of a thesis by Ducosté, who reported many demonstrative examples. Conscious impulsions to stealing, to self-mutilation, to incendiary acts and to exhibitionism have been reported at various times. Conscious and remembered impulsions to procursive acts, to wild pranks, to impulsive vagabondage and to ambulatory automatism were related by Heilbronner, in 1903, and Donath, in 1910. Similar reports have been received of examples of conscious epileptic impulsions to speak, to recite, to declaim, to cry or to injure.

The problem of remembered epileptic psychoses remains to be solved. This is not true of the mental disorders that follow convulsive attacks, in particular crepuscular forms, which justly owe their name to the more or less clear conservation of consciousness and to the more or less integral persistence of memory.

In conclusion, it may be affirmed today that aside from records of minor attacks of epilepsy and of mental disorders immediately following convulsive attacks there exist in medical literature relatively few reliable documents which demonstrate the conservation of consciousness and memory in the manifestations of common convulsive epilepsy and in those of latent psychic epilepsy. This statement, especially important as it concerns the conscious and mnemic impulsive equivalents, imposes therefore the greatest reserve in this respect in the discussion of diagnosis and the establishment of medicolegal conclusions.

Recent Advances in the Knowledge of the Pathologic Anatomy of Epilepsy: Extrapyramidal Epilepsy and the Epileptogenic Center. O. Crouzon.

Pathologists used to attach importance to lesions of the cornu ammonis in essential epilepsy. Bratz discovered such lesions in half of the cases of epilepsy that he studied and established them as sequelae of earlier, perhaps of fetal, lesions. Chaslin reported neuroglial sclerosis beneath the meninges, which he thought might be hereditary or due to developmental disturbances. Bleuler found such hypertrophy of the neuroglia fibers in the brains of twenty-six epileptic persons. A. Lubinoff, Borestine and Rosenstein found the lesions described by Chaslin in the fibers of the hippocampus and also vascular lesions. Hajos reported two types of lesions, sclerosis and cytoclastic degeneration, the cell being enclosed by astrocytes. In late epilepsy, André Léri reported a vermicular state with miliary sclerosis of the cerebral cortex. Alzheimer and his pupils observed gliosis in the molecular layer in 4 per cent [40 per cent? W. F.] of cases of essential epilepsy, with diminution of nerve cells and of myelin fibers in the second and third cellular layers. Alzheimer studied the neuroglia cell nests and described infiltration of the white substance by numerous compound granular cells. Cells of the Cajal type, related to anomalies in development, exist frequently in the molecular layer.

In six cases of essential epilepsy studied by Bertrand and Rives, architectonic alterations were frequent and diffuse. The lesions were not senile changes. The authors could not determine in what measure they were correlated with the gravity of the clinical condition and with what constancy such changes were encountered in essential epilepsy. In the most typical case there were profound disturbances of the cortical structure, consisting of neuronal disintegration with the formation of numerous acellular plaques disseminated throughout the cortex. Recently, Minkowski described vascular lesions characterized by hyperemia, recent thrombosis, perivascular dilatations of the small vessels and capillaries, with recent perivascular exudates, sometimes even infiltrates, and numerous hemorrhages in the perivascular spaces and in the nerve substance. Such lesions do not seem to explain the epileptic crisis, but they may play a rôle in the production of the disease.

Several studies of myoclonic epilepsy (Unverricht's syndrome) have appeared. In 1926, Angelo Cataleno found lesions of the dentate nuclei, and Clark expressed

the belief that myoclonic epilepsy is a syndrome caused by lesions of the cortex and of the midbrain. Lafora found amyloid corpuscles in myoclonic epilepsy. Krakora found similar amyloid bodies enclosed in the ganglion cells in an epileptic patient without myoclonia; he believed that these corpuscles are not characteristic of the Unverricht syndrome. Van Bogaert published a study on forms of myoclonic epilepsy differing from those of Lundborg and Unverricht in being accompanied by progressive choreo-athetosis. In two cases there were cortical degeneration, status marmoratus of the corpus striatum and variable lesions of the olivary bodies. Urechia showed that epilepsy due to syphilis may present not the characteristic lesions of neurosyphilis, but merely inflammation of the arterioles. Urechia published an observation similar to one reported by Jakob in which there existed only degenerative lesions; infiltrative lesions were lacking completely and in their place were some abortive manifestations of arteritis.

Altschul observed in persons with epilepsy alterations in the motor cells of the medulla—chromatolysis, fibrillolysis, pigmentation and amyloid bodies in great numbers, chiefly at the entrances of roots, even at those of the posterior roots. Clonic convulsions are generally believed to originate in the convolutions of the motor zone. Pitres, Frank and Nothnagel have stated, however, that epilepsy is not exclusively cortical; that centers productive of convulsions may exist in the medulla or in the brain stem. Later, a great influence in the development of the attacks was attributed to the vasomotor centers; Spielmeyer pointed out that the vasoconstriction which opens an attack may bear a relation to lesions of the cornu ammonis and of the Purkinje cells of the cerebellum. On the whole, modern observations seem to show that the clonic factor depends on the cerebral cortex but that more importance must be attributed to extrapyramidal motor paths and subcortical centers for the tonic element of the attacks. These centers are the globus pallidus, the corpus striatum, the brachium conjunctivum, the cerebellum and the red nucleus.

Study of the voluntary movements of patients with partial epilepsy by a graphic method has led to the conclusion that in partial epilepsy certain peculiarities of voluntary movement give the impression that an extrapyramidal element exists. Tonic spasms apparently of extrapyramidal origin have been observed in the course of convulsive attacks. Certain torsion spasms or attacks of spasmodic torticollis, accompanied or not by pallidal rigidity, point to the possibility of a striatal epilepsy characterized by simple syncopal forms, by convulsions that are chiefly tonic or by automatic acts. While epilepsy does not occur in the course of Parkinson's disease, the possibility of an alternation between the two diseases is admitted. Wimmer expressed the belief that epilepsy may result from a pathologic cooperation of the cerebral cortex with injured basilar ganglia, and numerous workers have claimed that the lesions occur not in the cerebral cortex but in the basal ganglia. A certain number of researches have indicated that epilepsy may have a ventricular origin.

Dilatation of the lateral ventricles is frequent in epilepsy, according to Thom. Of fifty-seven patients examined, thirty-one showed a cortical lesion with ventricular dilatation, sixteen presented only cortical lesions and fourteen showed only ventricular dilatation. Dilatation of the ventricles thus existed in 54.6 per cent. Since the cortical lesion was not sufficient as the sole cause of epilepsy, Thom concluded that the primary lesion must be sought in the white substance.

Albert Salmon, of Florence, in 1932, claimed that the cortical theories do not explain the pathogenesis of all cases of epilepsy. They do not explain epilepsy in decerebrate animals or in the new-born. There are a certain number of cases of epilepsy of striatal origin. Moreover, though the cortical theories explain a part of the phenomena of jacksonian attacks, they do not explain all the phenomena of diffusion in generalized attacks. There intervenes a vegetative syndrome, at first sympathicotonic, later vagotonic. The most important vegetative centers are in the infundibulotuberal nuclei, excitation of which may produce certain symptoms of epileptic attacks. These centers are probably sympathetic and are in close relation with the vasomotor subthalamic and bulbar centers. Salmon questioned whether

these sympathetic diencephalic centers do not constitute one of the pathogenic elements of epileptic attacks, and he furnished experimental and clinical data in support of this idea: 1. The injection of potassium chloride into the infundibulum by Demole caused convulsive crises with mydriasis and muscular hypertonia. The injection of potassium chloride into the wall of the third ventricle and into the lateral ventricles by Marinesco, Sager and Kreindler caused convulsive crises with profound sleep. Epileptic phenomena were observed by Morgan after the injection of silver nitrate into the tuber cinereum. Definite alterations in this center were established at autopsy in cases of epilepsy. 2. Clinical investigations support these experiments. Hypertension in the third ventricle provokes loss of consciousness and tonic convulsions. Tumors of the third ventricle, as well as tumors of the hypophysis, give rise to epileptic attacks. Epileptic attacks may arise in connection with functional disorders of the hypophysis. Ameliorations of epilepsy by treatment with pituitary have been reported, and considerable diminution of the pituitary secretion in the spinal fluid of persons with epilepsy has been observed. Autopsies seem to confirm a connection between the hypophysis and epilepsy.

Because of the anatomic and physiologic connections of the hypophysis with the infundibulotuberal centers, one may admit the hypothesis of an epileptogenic center in the diencephalic region. From the exposition given, it seems probable that hypophyseal insufficiency predisposes to convulsive crises. By reason of the close relations of the pituitary gland with the genital glands, the thyroid and the suprarenals, hypophyseal insufficiency has been considered to explain the frequency of epileptic crises when there are modifications of these glands.

How shall one explain the production of crises by meningocortical lesions? It may be through quantitative and qualitative modifications of the cerebrospinal fluid. Many authors in cases of cortical epilepsy have established alterations of the cerebrospinal fluid which may also react on the infundibulotuberal nuclei. This center is highly sensitive to modifications of the cerebrospinal fluid, as may be seen in crises in cases of cerebral tumors, serous meningitis and choroidal alterations and also in attacks of anaphylactic origin. Nevertheless, even if the mechanism that has been described explains the vegetative syndrome, how can one explain the convulsive movements? They are explained by the functional bonds which unite diencephalic and mesencephalic sympathetic centers with the subthalamic, mesencephalic and bulbar vasomotor centers. Moreover, hypersecretion by the pituitary gland and hypersecretion of the cerebrospinal fluid itself may have a convulsant action.

PRESENT STATUS OF THE TREATMENT OF EPILEPSY. O. CROUZON.

Physicians are no longer limited to treatment with bromides, and it is superfluous to discuss the results obtained with phenobarbital. Phenyl methyl barbituric acid has been reported by Maillard and Renard to be as efficacious as phenobarbital without producing any of the objectionable effects observed with the latter preparation. The results in cases of intellectual confusion are equally good.

When epileptic patients at the Salpêtrière refused to use bromides further, Pierre Marie, Crouzon and Bouttier employed sodium borate and then potassium borotartrate from 2 to 3 Gm. daily, with gratifying results. The attacks diminished in violence and were frequently reduced to a momentary unconsciousness, a fall or some brief movements. The effect on the number of attacks was notable. Roubinovitch placed phenobarbital and bromide before potassium borotartrate in order of efficiency but stated that potassium borotartrate has none of the objectionable qualities of the other two and may be combined with them when intolerance develops.

An opium and bromide mixture and bromide with phenobarbital digitalis, belladonna, atropine or pilocarpine have also been successful. Forty per cent of epileptic patients who are resistant to treatment with phenobarbital may react favorably to a daily dose of from 4 to 6 tablets each containing 5 cg. of phenobarbital and 0.25 mg. of all the alkaloids of belladonna. Intraspinal injections of benzoyldimethylamino-ethylpropanol hydrochloride have been recommended by

Giacomelli. Intravenous injections of cholesterol have been used with encouraging results. Ipecac has been employed as a remedy for the confusion that follows epileptic attacks and is frequently accompanied by digestive disorders. Lépine reported attempts to desensitize epileptic persons by intradermal injections of tuberculin. Cobra venom, rabies virus and antidiphtheric serum have been used successfully. Ceni favored specific antiepileptic serotherapy, injecting progressively increasing doses every three or four days; the serum of other epileptic persons or that of the patient may be employed. Rossello showed that soluble salts of calcium by subcutaneous injection have a remarkable effect. Parhon and Cahane obtained good results after daily intravenous injections of 10 cc. of a 10 per cent solution of calcium chloride.

F. Machon and others have proposed the intramuscular injection of milk; they have obtained some amelioration, especially in children. In Germany a combination of milk with a small quantity of hypervirulent bacterial albumin (*Xifalmilch*) has been used. Autochemotherapy has given some results, but they are not highly encouraging. Autoserotherapy, in the form of injections of the contents of blisters, employed by Tinel has given some good results. Gordon attempted to treat epileptic patients by injections of their spinal fluid and has obtained some temporary results.

Opotherapy may be usefully employed only as an auxiliary remedy in certain cases. Ovarian substance has caused improvement in some cases of catamenial epilepsy. Thyroid has given good results in some cases but uncertain or no results in others. Pluriglandular therapy may be a useful adjuvant to treatment by drugs; it may overcome the depression that may be observed in the course of treatment with bromide. Under malarial therapy, epileptic attacks have ceased during the fever and during the following months, but they have begun again afterward.

Before starting any rigid regimen or hygienic method, the organism should first be put in the best balanced condition. Jean Lépine recommended physical exercise, without overstraining the heart, life out of doors and a nontoxic diet of modest quantity, milk, vegetarian, or mixed, low in nitrogen. Avoidance of all exciting drinks and of certain foods is desirable. De Fleury prescribed the elimination of meat from the diet and forbad the administration of diuretics and of lactic ferments. A salt-free diet combined with treatment with bromide has also been advocated. Pagniez and Plichet have insisted that a ketogenic diet should be followed as strictly as would be a regimen for diabetes. Bread, starchy and sweet foods are replaced by fats and oils, and the intake of protein is low. Before commencing the regimen, the patient is given a liquid diet for forty-eight hours. On the second day, if hunger is too great, a salad seasoned mainly with olive oil is given at noon and at night. Constipation is combated with magnesium oxide, liquid petrolatum and castor oil. The administration of sedatives is continued.

These methods of treatment are considered to act through the acidosis which they produce in the organism. This hypothesis agrees with investigations that have established a certain degree of alkalosis in epilepsy. According to others, the absence of crises during a ketogenic regimen is due to a considerable elimination of fixed bases and dehydration of the organism.

American authors have developed new facts as to the rôle of hydration in the genesis of convulsive paroxysms and the anticonvulsive effects of a maximum reduction of fluid. Study of the metabolism of water in epileptic patients has shown a tendency to retain water. When a copious diuresis follows the attacks, they are temporarily arrested, owing to the dehydration that changes the condition of the cerebrospinal fluid. The statistics of Temple Fay, of Philadelphia, an ardent advocate of dehydration, cover twenty-two cases observed for two and one-half years. The cases were selected because of the frequency and gravity of the attacks. Some patients who had had from twelve to twenty attacks per month had only one after treatment; others did not have any. A child who had had from one hundred to one hundred and fifty attacks per month had from nine to fifteen. The gravity of attacks diminishes, and severe attacks may be transformed into petit

mal, psychic disturbances or vagaries of character. Hartenberg, whose results are analogous to those of American authors, thought that the dehydration may act later in modifying the circulation of cerebral centers by lessening the volume of blood and acting through an unknown mechanism on the cerebral neurons, which are thus rendered less irritable. Several authors have expressed the belief that the dehydration acts by lowering the intracranial pressure; encephalograms of epileptic patients commonly show accumulations of fluid in the cortical subarachnoid regions. Pagniez remarked, however, that variations of the intracranial pressure in epileptic patients are not subject to fixed rules and that lumbar puncture exercises no effect on the evolution of attacks.

In young epileptic patients one should consider undertaking treatment for the following causes: (1) intestinal worms; (2) hereditary syphilis (by mercury, arsenic or bismuth); (3) birth traumatisms; (4) infections and intoxications reacting on the brain; (5) spasmophilia, or the hypocalcic syndrome (by the administration of salts of calcium and the application of ultraviolet rays). To these etiologic therapeutic measures should be added hygienic and medicinal (bromide, borax and phenobarbital) therapy. In treating the eclamptic syndrome, chief care should be given to the elimination of poisons from the organism by diet, intestinal enemas, sweating, bleeding and the use of chloral hydrate or chloroform.

Collins favored mercurial therapy not only in epilepsy due to syphilis but in other cases. Mercury seems to influence the glandular system by producing mobilization of calcium salts from the bones. Perhaps one may invoke the action of calcium on the nerve cells and also that of mercury on the nervous system.

Surgical intervention is indicated when there is reason to suspect a depressed fracture, an exostosis, the presence of a foreign body or a circumscribed meningeal adhesion. In numerous cases operation has been performed with success, but Sicard's repeated trephinings should be avoided. The remote results of surgical treatment in jacksonian epilepsy were studied by Leriche, of Strassburg, who believed that epilepsy is always due to the presence of a cortical focus or scar. In the vicinity of a fibrous cerebral cicatrix there is abnormal neuroglial proliferation. Treatment should contemplate the excision not only of the fibrous meningeal cicatrix but of the fibroneuroglial scar. Because of the difficulty of excision the treatment may be completed by roentgenotherapy. Operations for continuous jacksonian attacks have sometimes been successful, and convulsions due to circumscribed cerebral tumors may be cured by operation.

If some particular focus is suspected in a case of essential epilepsy, excision of the cortical area may be beneficial. In infants operation is usually useless. Various operations, such as ligation of the carotid arteries, sympathectomy and stripping of the carotids, have been tried with variable success. Ovariectomy seems to have an augmenting effect on epilepsy, but the treatment for epilepsy by ablation or by irradiation of the suprarenal glands has been practiced in Germany. Other abdominal operations have proved useless. Hydro-electric baths, transcerebral ionization and cervical galvanization have been used. Roentgen therapy has not given any favorable results to some, but others have found it successful. Barré and Metzger observed good effects from roentgen therapy in a case of jacksonian epilepsy of undetermined nature; after two treatments, the attacks, from which the patient had been suffering for about five years, ceased, and they had not reappeared four months later.

The treatment for status epilepticus is varied. Primarily, all excitement should be avoided; there should be little heat and light; the patient should be prevented from speaking much when consciousness returns. Bromide, phenobarbital and tartrate in large doses, injections of solution of chloral hydrate, small doses of scopolamine, inhalations of chloroform, bleeding, lumbar puncture and colonic lavage have been advocated. Desruelles and Agnès Chiarly, in 1931, called attention to the efficacy of intravenous injections of a hypertonic solution of a bromide. In cases of continuous or frequent attacks they injected 10 cc. of a 10 per cent solution of potassium bromide. They expressed the belief that it would be practical to use a 20 per cent solution of phenobarbital by intramuscular injection. Subcutaneous or intravenous injections of a barbital derivative have been used to arrest

status. Paraldehyde has also been reported as ameliorating this condition. Phenobarbital sodium injected intraspinally in doses of 10 cg. has been employed. Some workers prefer to make the injections via the atlanto-occipital path and the cerebral arachnoid spaces, using 22 cg. in 2 cc. of distilled water. Though this therapy has increased the intervals between attacks, it is likely to cause accidents. Amaducci reported three cases of transitory facial paresis as a result of this method. Among sedatives may be mentioned hypodermic injections of from 3 to 5 Gm. of amylene nitrate. Petzetakis advocated intravenous injections of calcium chloride, in 5 per cent [50 per cent? W. F.] solution, in doses of from 5 to 10 cc. Other authors have obtained a notable reduction in the number of attacks by injecting 50 mg. of acetylcholine every other day.

PRESENT STATUS OF THE SOCIAL QUESTIONS. O. CROUZON.

Article 64 of the Penal Code declares: "There is neither crime nor misdemeanor when the accused was in a state of dementia at the moment of the action or when he had been constrained by a force which he was not able to resist." The word "dementia," which pathologically applies to certain exact states, is here employed in a broad sense and refers to all mental disease that alters the judgment or the will. With epileptic dementia there is evidently no responsibility, but in attempting to estimate the responsibility of epileptic persons in regard to crimes, misdemeanors, assaults, theft and outrages against decency it must first be determined whether the act was committed in a lucid moment (if so, the modifications that epilepsy may bring to the mental state of the patient must be considered) or as an epileptic aftermath. In epileptic equivalents, when there is loss of consciousness with amnesia on awakening, the acts are committed in a sort of automatism and are always accompanied by confusion. When the acts of an epileptic patient are remembered, there are difficulties in knowing whether he thoroughly realizes in the lucid period what he has done or whether there is not a permanent mental basis for the conclusion of complete irresponsibility.

When crimes are committed during paroxysmal attacks they should be looked on as equivalents if the following characters are present: suddenness of onset and bruskness of termination, brief evolution, retrograde amnesia, exhaustion, repetition of attacks under the same form and favorable influence by treatment. The actions are independent of exterior circumstances, especially as concerns what the patient does or thinks at the instant preceding the act. They are often in discord with the habitual tendencies of the subject, have no appreciable motive and are out of all proportion with the object attained; they are followed not by remorse or cynicism but by dejection or astonishment. The person who has committed a crime during an equivalent has acted in a typical state of dementia. The experts' decision will be irresponsibility. Should the expert decide for internment? If the subject was in a state of dementia at the moment of action but is no longer so at the moment of examination, he should not be interned, but he should not escape all surveillance. He should be kept in appropriate surroundings where he will be constrained to follow hygienic rules and receive the treatment necessary for his condition. In cases of crimes or misdemeanors committed in intervals between paroxysms, the expert must determine whether the misdemeanor was conditioned by the mental state and whether the mental state was such as to weaken or annul responsibility.

A delinquent epileptic person may be sent to a prison or to a mental hospital or may be given his liberty; none of these solutions, however, seems satisfactory. Nondelinquent epileptic persons have at their service only an asylum or a hospital, and as the number of beds in hospitals is limited, confinement there is difficult. Legrande du Saulle said in 1878: "To place an epileptic person in a safe place where he is definitely secure, I am obliged to place about his shoulders the cloak of delirium." There is then great need not alone of reforming the penal rules, of individualizing punishment, but of insuring assistance to nondelinquent persons with epilepsy. Berthelémè's conclusions may be summed up thus: Independent of an attack, entire responsibility; during an attack, irresponsibility. Ceiller, in

summing up a report on penal responsibilities and the confinement of delinquent or criminal epileptic persons claimed as most urgent the creation of psychiatric annexes to prisons to permit complete observation of the subject and a record of his attacks. Measures must be taken early, because epileptic persons are often led to delinquency by the impossibility of honestly earning a livelihood.

For treatment and rehabilitation of persons with epilepsy, colonies may be created which include: (1) a department for insane persons with epilepsy; (2) a hospital department for noninternable epileptic patients unable to pay or to work; (3) a place of reeducation for delinquent persons and criminals; (4) schools with special instructors and well established programs; (5) centers of apprenticeship; (6) industrial centers for adults, and (7) agricultural centers. These centers, besides offering treatment, may procure useful and remunerative work for all epileptic patients.

In Belgium, the organization is the most perfect. In Sweden, it would be best to create two kinds of colonies, penitentiary colonies and hospital colonies, in both of which the treatment should be based on work. Article 489 of the Civil Code regulates the civil rights and duties of epileptics: "The person of age who is in a state of habitual imbecility, dementia or fury, is incompetent even when his state presents lucid intervals." The testimony of epileptic patients should therefore be accepted with great care and prudence. Moreover, testamentary capacity should be judged carefully.

The marriage of epileptic persons must be considered from two points of view: 1. Marriage is not interdicted as far as the patient is concerned, but the recommendation to avoid sexual excesses should not be forgotten. 2. As far as descendants are concerned, traumatic epilepsy cannot have any influence. Epilepsy is most frequently to be considered as accidental and without any hereditary or familial character. In Sweden and Finland marriage of epileptic persons is forbidden; however, the patient may be given the choice between renunciation of marriage and sterilization to avoid procreation.

The degree of incapacity resulting from war wounds or industrial accidents may be calculated on the basis of the number of attacks during each month and the temporary incapacity which they provoke. Cases of severe epilepsy are reckoned as producing from 85 to 100 per cent disability. Persons injured in civil life or in war in whom epilepsy has developed often have great difficulty in obtaining work. The pension accorded such a person is insufficient without further income; moreover, it is wise not to leave the patient inactive. It seems desirable to have agricultural colonies in which preference is given to invalids and in which patients may be employed while receiving appropriate treatment. For epileptic persons without mental disturbance, it is necessary to organize family care as is now done in Belgium and Scotland. It is always beneficial as well as useful to have epileptic patients work, but the work should be in connection with instruction and education in special establishments. Unfortunately, there are few asylums for epileptic patients in France. There are a few beds at the Salpêtrière in Paris and at Bicêtre and private asylums dedicated to the care of these patients at Tain, La Force and Blois. In Germany, there is a community of Christian epileptic patients at Bielefeld, who work in common and have ceased to be a charge on or danger to society. Another community at Biesdorf, near Berlin, includes more than a thousand patients. In England there are large agricultural colonies. Epileptic persons who are delinquent are interned at the prison of Wakefield, where they are put to useful work and given psychotherapy, including both mental and moral education. In the United States there are colonies in many states in which children receive instruction and adults are occupied in various ways. In Holland there exists a hospital for research on and treatment of epilepsy. There are also colonies in which patients follow as nearly as possible their own professional knowledge and habits. In many other lands in which there are no organizations so complete there is a tendency to provide analogous aid, as in Spain, Italy, the Argentine Republic, Portugal, Sweden and Russia.

Paul Boncour studied the handling of epileptic children of school age and came to the conclusion that the social adaptation of epileptic persons and their work are the more perfect the earlier they begin to study or work as an integral part of the social plan. The following rules have been set up: 1. An epileptic child should work. 2. The time of work should be decided for each patient, taking into account his mental state, the evolution of the disease and the number and duration of the convulsive seizures. Epileptic persons showing extreme backwardness should be subjected to special rules conforming to the principle of professional orientation of abnormal persons. All intellectual work should cease during the paroxysmal periods. The program of instruction should be established during the intervening periods. If these are sufficient, the regular program for a normal child of the same age may be used. If the crises are exclusively nocturnal, the child may attend the ordinary schools. If not, he should be sent to a class for the training of abnormal children. Only epileptic persons who are very severely afflicted and those who are demented should be in asylums. Knowledge should be sought with regard to all organizations for internment with centers of occupation for teaching abnormal persons of all kinds, where epileptic persons may be kept and taught some trade or work suitable to their condition.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 27, 1933

A. C. Buckley, M.D., *President, in the Chair*

A Case of Pernicious Anemia and Amyotrophic Lateral Sclerosis. Dr. Alexander Silverstein and Dr. Louis Soloff.

The association of combined degeneration of the spinal cord due to anemia with coexisting disease of the anterior horn cells is of particular interest.

Report of Case.—A. S., a white man aged 64, who was admitted to the Temple University Hospital on Aug. 8, 1933, had been in good health until about a year before, when he began to experience weakness in the right arm in lifting. The weakness gradually progressed, affecting mostly the movements of the shoulder; it was followed by wasting of the muscles of this region. Three or four months later, the left arm became similarly afflicted. For a few months before admission, he had slight difficulty in swallowing and occasional trouble with speech; he was unable to pronounce words properly, although "he knew what he wanted to say." In the beginning he had a dull pain in the shoulders and arms, which, however, did not annoy him. Other than this, there had been no subjective sensory complaints. Since the onset of the illness he had lost 30 pounds (13.6 Kg.) in weight, partly because he was not given proper food. He had also had "swollen ankles."

Examination: The patient was poorly developed, mentally clear and cooperative. The face had a brownish hue. There was marked weakness of both arms, affecting the muscles of the shoulder most, those of the elbow less and those of the hand least. Abduction, adduction, flexion and extension in the region of the shoulder were affected, there being practically no voluntary movement. The flexor muscles of the forearms were greatly involved, whereas the extensor muscles were less involved. The dynamometer registered 25 in each hand; compared with other parts of the arm, the weakness was mild. There was severe atrophy of the entire shoulder girdle on both sides, there being little muscle tissue in this region. The wasting was also well advanced in the muscles of the arms and thorax, but there was little involvement of the muscles of the hands. The legs did not show any disturbance; the musculature was well preserved. Fibrillations in the wasted muscles were widespread, the fascicular twitchings resembling what has been called "muscle madness" (*folie musculaire*). These movements

were spontaneous and were seen mostly in the shoulders, thorax and forearms, although to some degree also in the thighs and the calves.

The jaw jerk reflex was present. The right ankle reflex was prompt; the left was lost. The pectoral reflexes were greatly diminished on both sides. The biceps reflex was absent on the left and greatly diminished on the right. The patellar reflexes were very active on both sides. The right achilles tendon reflex was present; the left was greatly diminished. The abdominal reflexes, although present, responded feebly.

Vibratory sense was preserved in both the arms and the legs, but there was a quantitative diminution in the legs as compared with the arms. All other sensations, such as pain, temperature, muscle position and passive motion, graphesthesia and stereognostic perception, were normal. Station and gait showed no spasticity or other abnormality.

The olfactory sense was normal; the fundi were normal except for some evidence of arteriosclerosis. There was mild bilateral proptosis; the pupils were 3 mm. in diameter and responded promptly to light and in accommodation. There was no evidence of ocular or facial weakness. The corneal reflexes were preserved, and the sensory and motor components of the fifth cranial nerve were intact. The tongue showed many coarse fibrillary twitchings and tended to protrude to the right, with marked tremors. There were a few small areas at the edge of the tongue that suggested early atrophy.

The uvula was in the midline; the palatal and pharyngeal reflexes were present. Laryngeal examination showed that "abduction and adduction are normal but tension is markedly impaired, causing the cords to flap and vibrate unevenly."

Laboratory and Special Studies: The Wassermann reaction of the blood and spinal fluid was negative. The spinal fluid was clear, colorless and under a pressure of 10 mm. of mercury. The blood picture on August 8 was: hemoglobin, 5 Gm.; color index, 1; red cells, 1,340,000; white cells, 4,500; neutrophils, 54 per cent; eosinophils, 5 per cent, and monocytes, 3 per cent. There was also marked anisocytosis, with slight achromia and poikilocytosis. The blood count on August 19, was 940,000 red and 2,400 white cells; hemoglobin was 4.5 Gm., and the color index, 1.4. The picture was that of megalocytic anemia, probably pernicious anemia. Gastric analysis revealed complete achylia and no occult blood. Gastro-intestinal and roentgen studies gave completely negative results. The volume index was 1.4; the reticulocyte count, 2.4; the platelet count, 68,000. The icterus index was 15. The result of the van den Bergh test was moderately strong and delayed. The urobilinogen test was positive in a dilution of 1:40. Liver therapy was begun, and the therapeutic test was positive, the reticulocyte count rising rapidly within ten days to 21.9 per cent.

Course: Under intensive treatment for pernicious anemia, including intramuscular injections of liver extract, the patient made remarkable improvement generally. He felt stronger; the brownish discoloration of the skin disappeared, and the face was bright red. On September 18, the red cell count was 3,300,000; the white cell count, 8,100; hemoglobin, 10.5 Gm., and the color index, 0.9. Anisocytosis and poikilocytosis were still marked; megaloblasts were absent. The neurologic picture remained the same, except that the patellar responses had become more exaggerated, without evidence, however, of pathologic reflexes.

Comment: The case was evidently one of amyotrophic lateral sclerosis with unusual distribution. The diagnosis of pernicious anemia was questioned because of the absence of subjective or objective sensory disturbances. We believe that there were two distinct conditions. The primary pernicious anemia was coincidental, just as pneumonia, tuberculosis and dermatosis coexisted in Wilkinson's series of 370 cases.

DISCUSSION

DR. WILLIAM G. SPILLER: The case is unusual in two respects: The amyotrophic lateral sclerosis was not of the distal but of the scapulohumeral type, and it was associated with another disease of the spinal cord, pernicious anemia. The occurrence of two diseases of the spinal cord in the same person is not unknown.

I have made the clinical diagnosis of tabes and syringomyelia in the same person, and necropsy showed the diagnosis to be correct. H. Schlesinger reported a case of this kind and gave me sections of the spinal cord from his patient. More recently, Winkelman and Eckel published a paper citing a number of similar instances. In 1905, Camp reported from my service the occurrence of tabes with severe anemia. The spinal cord showed the lesions of tabes and other changes suggestive of anemia. In the July, 1933, issue of the *Revue neurologique* (**2**:25, 1933), Dagnelie and Cambier emphasized the occurrence of sensory symptoms, especially subjective, in amyotrophic lateral sclerosis, and attributed them to involvement of the spinothalamic tract. The pain in this disease may sometimes be attributed to overuse of fatigued muscles weakened by the disease. In the case reported by Silverstein and Soloff the pain was in the shoulder, and the muscles of this part were greatly wasted and did not properly support the shoulder joint. Recently, degeneration of the anterior horn cells in posterolateral sclerosis of the anemic type was reported by Foerster, Hofheinz and Guttmann.

DR. N. W. WINKELMAN: The main question is whether pernicious anemia is the basic factor in the production of a neurologic picture which is not typical of amyotrophic lateral sclerosis. One of the strongest points against this possibility is the fact that, despite the marked improvement in the general picture of pernicious anemia, there was progression of the muscular condition. I realize that treatment with liver and hydrochloric acid is not always sufficient to produce complete relief from the neurologic symptoms referable to the spinal cord, but usually the progress of the symptoms is stopped. One sometimes sees, as in a case that I studied recently, severe disease of the motor cells in the anterior horns in pernicious anemia. It is infrequent, however, to have a symptom complex such as is presented by this patient.

MULTIPLE CARCINOMA OF THE BRAIN WITHOUT OBJECTIVE NEUROLOGIC SYMPTOMS. DR. ALFRED GORDON.

In malignant cerebral metastases there are two possibilities: Either the cerebral tissue alone is involved, or the meninges alone are invaded. The first type of involvement probably follows the arterial route; the second, the cranial nerves by means of the surrounding lymphatic vessels. There are also cases in which the meninges and the brain tissue are simultaneously involved. In the majority of cases the metastatic infiltrations are diffuse, without any special predilection for different areas of the brain. When there is metastasis to the brain there is usually widespread involvement of various organs and tissues in the body. In the majority of cases there are objective motor or sensory disorders, as well as involvement of the cranial nerves. In a smaller percentage of cases mental disturbances of slight intensity may be present, such as dulness or stuporous or confusional states.

The diagnosis of metastatic invasion of the brain is not always easy. It is often difficult to distinguish a secondary from a primary invasion of the brain.

The case to be described presents several features of special interest. Pathologically, it shows that carcinomatous metastases may be confined to the gray matter of the cortex. In my case only the cortex was invaded, not the basal ganglia. The other anatomic peculiarity is that the small carcinomatous masses were distributed exclusively over the rolandic convolutions and superior parietal regions of both hemispheres, more on the right than on the left. Identical formations existed over the lateral hemispheres of the cerebellum; four were on the right and two on the left side. No such pathologic structures were found on the cut surface of the cerebellum.

Clinically, there was absence of objective neurologic symptoms, in spite of the invasion of the sensorimotor area on both sides and the hemispheres of the cerebellum. The symptoms were purely of a mild mental and emotional character, namely, some confusion, extreme restlessness, insomnia, general nervousness and frequent vomiting.

Limitation of the metastatic formations to the cortex may be explained by the anatomic peculiarities of the cortical blood supply: the existence of short and long arterioles, the first distributed over the cortex and the second penetrating the subcortical layers of the white matter; the characteristic smallness of carcinomatous cells, and the terminal character of the arterioles.

The clinical aspect of the problem presents some difficulty. The metastases, while small, were sufficiently large to produce localized symptoms. Ten metastases were present altogether in both the rolandic convolutions and the superior parietal regions. I am inclined to believe that the absence of neurologic symptoms was probably due to the superficial character of the lesions; the underlying subcortical substance was not reached. The superficiality of the metastasis over the cortex of the cerebellum may, I believe, explain with a certain degree of probability the absence of ataxia and other cerebellar disturbances.

DISCUSSION

DR. D. J. MCCARTHY: Years ago (about 1908), Dr. Meyers and I reported a case of carcinomatous meningitis metastatic to carcinoma of the breast. The clinical diagnosis was cerebral syphilis. Pathologically, the meninges were covered with carcinomatous lesions. The cerebellum and cranial nerves were not involved. There were thousands of small foci of carcinoma in the pia-arachnoid, from 1 to 3 mm. in diameter.

PERSONALITY CHANGES FOLLOWING ENCEPHALITIS. DR. FREDERICK H. LEAVITT.

The case to be reported is of particular interest because of the complete change in personality or loss of identity which followed an illness that appeared to be acute encephalitis, either postinfluenzal or "epidemic." The alteration of personality persisted for six months and was dramatically dispelled by nitrogen monoxide anesthesia, given for the purpose of reducing contractures in the achilles tendons. The question is whether this depersonalization was a hysterical amnesic "cut-out" or a real personality change following encephalitis.

The patient, a probationer nurse, aged 20, of Irish parentage, is the third of four children. The oldest child was killed in an accident at 18; the others are living and normal. The family is emotionally stable. The patient's birth and development were normal. She graduated from high school at 17 and entered training when 19. For two weeks prior to Dec. 31, 1932, she had what she thought was a "grippy cold" and complained of headache, vertigo, fever, mental dulness and malaise in the head, neck and back. As she was a probationer she decided that she would not report "off duty" because she thought it unwise to lose time for illness. As she was of slight build she feared that she would not be accepted for training at the end of the probationary period. On the evening of December 31, she felt particularly bad and remarked to the head nurse that for two days she had had double vision and that vision was distinctly blurred. As she had fever she asked to be excused from duty; when she reached her room she collapsed. Following this, she was somnolent for a number of days and then had insomnia.

When I saw her on Jan. 5, 1933, I made a diagnosis of "postinfluenzal encephalitis." She was unable to raise her body from the bed or her head from the pillow. She could use both arms and legs while lying in bed but had marked fatigue in the extremities. On January 12, a combination of symptoms developed which persisted for over two months. The weakness in the legs had become practically complete paralysis, and there was weakness in the arms. Bilateral ankle and patellar clonus were present. A considerable degree of atrophy of the muscles of both arms and legs was noticeable. About the middle of March, there was pronounced weakness of the muscles of the throat, and it was difficult for her to swallow or to talk. Intense sweating of both arms and legs was almost constant and of such severity that the bedclothes became wet. Contractures of

both achilles tendons developed. During the acute phase, the pupils were widely dilated, but they reacted well to light and in accommodation. No abnormalities of the fundi were observed; no visual or extra-ocular disturbances occurred other than those noted at the inception of the disease. The Oppenheim and Babinski signs were absent, and there was no loss of control of the sphincters. Laboratory examinations shed no light on the etiology of the condition. Leukocytosis, with from 12,000 to 15,000 white cells, was reported from the beginning of the disease until March 9, when oophorectomy on the right side, suspension of the uterus and appendectomy were done. No infection of the genital tract was discovered. For this operation general ether anesthesia was used, which had no effect in altering the personality.

When the patient became stronger and was able to talk, she behaved strangely. She had apparently complete loss of recognition of all persons she had known before with the exception of her mother, who had remained constantly with her from the beginning of the illness. She showed no recognition of the physicians and nurses with whom she had associated and did not remember their names. She acquired an entirely new set of friends and associates during the six months of depersonalization. She had a loss of identity and denied her own name; she would reply, "No, I am Kay." She did not remember her brother or any of the incidents of her life prior to the illness. Former avocations were ignored. An interesting feature was the unique manner of talking that developed after the period of aphonia. It resembled "Pennsylvania Dutch" so much that inquiries were made as to whether she had associated with people of that stock either in her family or among her friends; it was found that she had not. Some of her expressions are illustrated in the following verbatim report:

Nurse: What are you laughing at?

Patient: It did down fall on you and you did not know.

Patient: Dr. Lover (Dr. Leavitt) said he was going to bring him in to me see (meaning Dr. Burr).

Patient: It is night getting to be? Could I please the bed pan have? Up me put please. (When given medicine) I don't do want it; you would take and let me see what you do. If to sleep I cannot go, can I sleep?

Nurse: Did the cat sleep well last night? (meaning a toy cat.)

Patient: He do not sleep; he not people be.

Patient: Doctors do funny be, but I am going a doctor to be. Can they not all say something and not the others say something else? They do at me poke and at me cut and do not up get me, but I do them like.

For a week during this period she stopped talking and appeared depressed and physically weak; this condition gradually disappeared and speech returned in the same unique manner.

On June 13, under nitrogen monoxide anesthesia the contractures of the achilles tendons were broken and plaster casts were applied. When the resident physician saw the patient two hours later, he noticed a complete change in the manner of talking, tone of voice and facial expression. She recognized the physician and all former friends and associates, calling them by name. When asked how she was, she said, "Very well, I must have been asleep." She stated that the last thing she remembered was the afternoon of Dec. 31, 1932, when the head nurse asked about her cold. She was mystified to discover that the trees were in full leaf, because when she last remembered them it was midwinter. She remembered her correct name and was much concerned as to whether she would be able to use an overnight pass for New Year's Eve that she was to have received. She said, "I am very much mystified because I remember being on duty in Maternity and then awakening on the table in the operating room." The peculiar style of talking had disappeared; she spoke in her usual manner. She stated that she had no recollection of anything that took place between Dec. 13, 1932 and June 13, 1933. At the time of this report, five months later, the same memory "cut-out" exists.

Since July, physical recovery has been pronounced. The plaster casts were removed from the legs; within a few weeks the patient was able to stand, and

the power to walk gradually returned. At present she is able to walk well. The only organic neurologic sign that is still present is ankle clonus on the left and abortive ankle clonus on the right. Her chief concern at present is when she will be able to return to duty at the hospital. Mentally, she is alert, and her personality is the same as before the illness.

The questions are whether this is a hysterical "cut-out" or an "alternating personality" and whether the contractures and paralyses were hysterical or the whole physical and mental picture was a postencephalitic dissociation situation.

DISCUSSION

DR. C. W. BURR: I saw the patient several times. The peculiarity of speech was unique. When I saw her first I asked her a question as I came in the room; her reply caused me to jump to the conclusion that she was of "Pennsylvania Dutch" extraction. After talking with her a little longer, I realized that the dialect was not "Pennsylvania Dutch" but that she was combining verbs, subjects and objects in most unusual sequence. I am convinced that she had encephalitis, either influenzal or epidemic, and I am also sure that the amnesia was real and not feigned. She undoubtedly continued to have true bilateral ankle clonus for many months; I have never seen this condition except in organic disease. Patellar clonus also existed for several months. I am not sure whether I should describe the condition as a mental state or a "personality change." The alteration in temperament and attitude toward life was not marked. The patient was not like the one of Morton Prince who was a devil in one personality, an angel in another and a criminal in a third. In this case, the friends and nurses with whom the patient became best acquainted while in the altered state were entirely neglected on recovery of the normal personality, and she returned to her old friends. This was not a case of mental confusion. In almost all the patient's speech it was easy to understand what she was trying to say; she merely mixed up the words, putting them in improper sequence. I do not say that I do not think the case was hysterical; it may have been.

DR. D. J. MCCARTHY: I do not doubt that the diagnosis of primary encephalitis is correct. I was not able to gather from Dr. Leavitt's report enough organic changes to make a diagnosis of encephalitis. Is a persistent true clonus rare outside of organic disease? I should expect other changes besides this. I believe that this was the only symptom to support a diagnosis of organic encephalitis. I think that it must be demonstrated that the patient did not have hysteria. The fact that she talked like a child, or made up thoughts, and then became normal after being anesthetized does not militate against a diagnosis of hysteria. Will Dr. Leavitt give a picture of the case from the standpoint of the findings which led him to make his diagnosis and also give a differential diagnosis? This condition covered a period of six months and then disappeared suddenly. It does not impress me as organic amnesia. I believe that the patient had a spastic condition of the arms which disappeared after she was anesthetized. The diagnosis could be made by hypnotizing the patient and seeing if one could resurrect memories of the period of amnesia.

DR. ALFRED GORDON: The disorder of speech reminds one of paraphasia. I recall many cases of organic diseases with such manifestations. This was one symptom of encephalitis in the present case. The second was the rigidity of the limbs, which is common in parkinsonism and postencephalitic conditions. Did Dr. Leavitt wait to see if the rigidity would pass off? Narcosis might have helped without an operation. Putting the phenomena together, it seems that the condition was postencephalitic parkinsonian rigidity of the limbs. The rigidity is suggestive of an organic but not of a functional type. Does Dr. Leavitt think that the brief mental disturbance is related to dream states? The patient was confused and disoriented and then became clear after narcosis.

DR. LEROY M. A. MAEDER: In the "Studies on Hysteria" by Breuer and Freud there is reported the case of a woman, aged 21, who suffered from hysterical

paralyses, contractures and disturbances of speech. She used a jargon of four or five languages. Later, she spoke English without apparently realizing it, at the same time understanding the German which was spoken to her. Still later, however, she did not understand what was spoken to her in her native tongue, German.

The young woman to whose condition Morton Prince devoted his book, "The Dissociation of a Personality," had in addition to her original or normal self three altered personalities which differed greatly and were often diametrically opposite each other in trains of thought, views, tastes, habits, experiences and memories.

DR. JOSEPH C. YASKIN: What has happened to the patient since her sudden recovery? Was there any change in the mental condition after the abdominal section? One is inclined to doubt the purely hysterical nature of the reaction. More than likely she had nonspecific encephalitis with transient change in personality. Viewed from this point, one can understand the sudden recovery.

DR. FREDERICK H. LEAVITT: I presented this case as one of depersonalization, either as a result of an infectious disease of the brain—encephalitis—or as a result of a hysterical dissociation. There were several psychic predisposing elements that might point toward the development of a hysterical dual personality. The organic neurologic symptoms seemed definite during the illness but disappeared after it, with the exception of the left ankle clonus. "Cutting" the tendons was not attempted, there being merely stretching of the contractured tendons and placing of the limbs in a plaster cast. In reply to Dr. McCarthy, the patient did have persistent ankle and patellar clonus, with marked wasting of the forearms and calves and intense sweating, but no Oppenheim or Babinski sign. In reply to Dr. Yaskin, ether was used during the laparotomy, and it had no effect in altering the personality state. Dr. Langdon stated that suggestive psychotherapy had been exerted just before the anesthetic was administered on June 13, and this may have had considerable bearing on the dramatic disappearance of the altered personality. Dr. Yaskin asked whether the girl has returned to training. I have advised her not to return for at least six months or a year, as her physical condition is not yet sufficiently good.

FOCAL ENLARGEMENT OF THE TEMPORAL BONE AS A SIGN OF TUMOR OF THE BRAIN: SECOND REPORT. DR. ROSS H. THOMPSON.

In a recent report, I described two cases of bulging of the squamous portion of the temporal bone due to an underlying tumor of the temporal lobe found at operation in young children. One case was the result of a meningeal fibroblastoma with cystic formation; the other, of a gliomatous cyst. The latter, by displacement of midline structures, had produced a milder degree of bulging in the opposite squama. In one case, therefore, the bulging was bilateral; in the other, unilateral.

The object of this report is to record and discuss three instances of bulging of the squamous portion of the temporal bone observed in adults, aged from 23 to 28, in each of whom an underlying tumor was found at operation. In two, evidences of organic nervous disorder were present in childhood.

CASE 1.—A man, aged 28, admitted to the service of Dr. William G. Spiller in the University of Pennsylvania Hospital, presented bulging of the squamous portion of the left temporal bone directly overlying a large cyst of the left temporal lobe, probably of gliomatous origin.

CASE 2.—A woman, aged 23, admitted to the service of Dr. W. James Gardner in the Cleveland Clinic, presented bulging of the squamous portion of the left temporal bone directly overlying a large cyst of the left temporal lobe; there was less marked bulging of the squamous portion of the right temporal lobe.

CASE 3.—A man, aged 23, also admitted to the service of Dr. W. James Gardner, presented fulness of the squamous portion of the left temporal bone and enlargement of the left side of the frontal bone and the mandible, and probably also of the zygoma and maxilla, with a fibroblastoma situated on the left lesser wing of the sphenoid bone.

DISCUSSION

DR. WILLIAM G. SPILLER: My interest in circumscribed bony overgrowth of the skull is not of recent origin. At least three distinct types may be recognized. At the April, 1899, meeting of the Section on General Medicine of the College of Physicians of Philadelphia I presented a man with an extraordinary enlargement at the top and side of one half of the head which aroused my interest. An operation resulted fatally. The brain, containing a tumor, was shown at the following meeting of the section in May, 1899. A report of the case was published in the *Medical Record,* May 27, 1899. This seems to have been the first case of hemicraniosis in the literature. Brissaud and Lereboullet's report was made in 1903. This form is suggestive of fibroblastoma.

A second form of hemihypertrophy of the skull and sinuses, which occurs with ipsilateral cerebral atrophy, was recently described by Dyke, Davidoff and Masson in the *Journal of Nervous and Mental Diseases* (**77**:68 [Jan.] 1933).

A third form was described by Ross H. Thompson in *The Journal of the American Medical Association* (**99**:379 [July 30] 1932). It consists of thinning of the squamous portion of the temporal bone and may be unilateral or bilateral. In this form the bone is not hypertrophied; the enlargement is produced by a pushing outward of the thinned temporal bone. Dr. Thompson reported two cases of this type, both in young children, from the neurologic service of the University of Pennsylvania. In one case it was possible to examine the squamous portion of the temporal bone, and it was found to be thinner than normal. This condition is suggestive of tumor of the brain at the site of enlargement, and is most likely to occur in early life, when the bone is more yielding. The tumor may be a glioma or of another type.

Dr. Thompson now reports three additional cases, one from the neurologic service of the University of Pennsylvania and two from the service of Dr. W. James Gardner, of Cleveland. These three cases were in adults and occurred with tumor of the brain, but the condition dated probably from early life. In one case hypertrophy of the bones of the face on the side of the enlarged temporal bone occurred and made the case different from the others. This condition must not be confused with minor differences between the two sides of the face which may be seen in normal persons, especially when such enlargement is not in relation to the squamous portion of the temporal bone.

DR. N. W. WINKELMAN: I believe that the only thing Dr. Thompson has omitted in his lucid description of the cases is the report of roentgen examination of the skull. I have been interested in the subject of bone enlargements of the skull, not only from the angle of the underlying endotheliomatous tumors but because frequently focal hyperostosis occurs in association with conditions other than fibroblastic tumors. Several cases of this sort come to my mind. One is that of a child in Dr. Fay's service at Temple University; the roentgen findings were typical for underlying endothelial tumors; at operation no such tumor was encountered, and microscopic examination of a bone revealed a picture typical of Paget's disease.

One must also consider among focal enlargements of the bones of the skull the ordinary osteoma, which is frequently the result of trauma, although trauma can be part of the history of the hyperostosis associated with underlying tumors, as has been already stressed by Dr. Spiller in his numerous contributions on this subject.

Dr. Thompson presents another type of lesion that may be associated with a bony enlargement; in his cases the temporal bone seems to be the site. One must, therefore, not jump at a conclusion that an endothelial tumor underlies a bony enlargement. One must, of course, be careful to eliminate cases in which there are irregularities in the skull which at times superficially resemble enlargements such as those described in this presentation.

DR. A. C. BUCKLEY: Was there any unusual relation between the temporal and the parietal bone at the squamous suture?

DR. WILLIAM G. SPILLER: I wish to say to Dr. Winkelman, and I think that Dr. Thompson will agree, that the enlargement of the skull in Dr. Thompson's third case was far beyond anything that could be considered as normal. There is often a great difference between the two sides of the face. But in this particular case the difference was so striking that I do not think it could be mistaken, though the condition might have been considered hypertrophy of the skull. An enlargement of the skull such as this in a patient who did not have an infantile lesion could not be considered within the limits of normal.

DR. ROSS H. THOMPSON: Many factors influence the shape of the skull. Schuller mentioned race, family characteristics, occurrences of intra-uterine life, the passage of the head through the birth canal and the habitual position of the head and body, especially during the first five years of life. He mentioned, further, the effect of the positions of the head peculiar to certain trades, and referred to the large skulls of those belonging to higher callings.

In answer to Dr. Buckley, Todd, Wingate and Lyon, who recently made a study of human skulls, stated that the years from 26 to 30 form the period of election for closure of sutures. During this time most of the union that is going to occur takes place. The exact dates for closure of sutures and the order of progress are to be found in the text (*Am. J. Phys. Anthropol.* **7**:325, 1924; **8**:23, 1925).

DEHYDRATION AND FLUID LIMITATION. DR. TEMPLE FAY.

The walls of the craniovertebral cavity are fixed after the fontanels have closed so far as ability to expand or contract temporarily is concerned. That small and inconsequential changes in volume may be produced by flexion and extension of the neck and trunk, is possible. The cranial cavity is filled with three distinct volume masses: (A) arteriovenous circulating blood; (B) nerve, meningeal, dural and vessel cells, and (C) cerebrospinal, perivascular and interstitial fluid. The sum of A, B and C equals the total volume capacity of the craniovertebral container at all times. Volumes A and C being liquids, are incompressible; volume B is practically incompressible, because of its high fluid content. It follows that once the container is filled there is no possibility of adding a single cubic centimeter of new volume without bursting the walls. Subtraction of an equal volume of one component must follow. These factors have long been recognized and form the basis of the Monro-Kellie doctrine.

The profound significance of this volume relationship is borne out by the following examples: 1. In subdural hemorrhage the excessive venous blood in the perivertebral and dural sinuses first gives way. Next, there is displacement of the brain, owing to loss or redistribution of the cerebrospinal fluid within the ventricles and the cisterns, as well as in the subarachnoid space. When this compensation limit has been reached, a state of increased intracranial pressure, as measured by the manometer, begins to arise. The arterial circulation is shut off, which is followed by anemia, anoxemia and death.

2. Edema, whether traumatic, toxic, allergic or metabolic, is characterized by a rapid shift of volume B in terms of swollen cells and an increase in tissue-bound fluid. Volumes A and C must compensate simultaneously and to an equivalent amount. Thus, the symptoms may be fulminating, owing to the large and rapid shifts of volume. Volume A, concerned with supplying sufficient oxygen and nutrition for conscious function, may be rapidly displaced to such an extent that deep stupor occurs.

3. Increase in cerebrospinal fluid volume, because of overproduction, improper elimination or obstruction in the circulatory pathways, is associated with the post-traumatic inflammatory or developmental processes. Increase in volume C depends on a compensatory decrease in volume A, which is concerned with the cortical circulation, and eventually there may be a decrease in volume B in the form of atrophy, shrinkage or hydrocephalic compression of the brain substance and its consequent diminution in size and secondary diminution in the need for vascular volume.

4. Hyperemia may occur from obstruction to the venous outlets or from intense generalized cerebral congestion. Increase in volume A must be and is compensated for, probably by a displacement of volume B and C, the latter being temporarily adjustable; the former suffers through disturbances in pressure and accumulation of fluids secondary to hyperemia. Localized or generalized punctate hemorrhages and intramedullary hemorrhages must be considered in the aggregate as types of blood tumors. When hyperemia is associated with local or generalized edema, the difficulties discussed in the first and second considerations are combined, and a condition is usually encountered which is beyond clinical assistance.

The changes in volume already considered include the majority of pathologic processes within the craniovertebral cavity. The symptoms which arise depend on one or a combination of the disturbances in volume relationships. From the standpoint of a logical attack on such problems, the solutions are concerned with: (1) enlarging the craniovertebral cavity, or "decompression;" (2) withdrawal of "available" cerebrospinal fluid by ventricular, cisternal or lumbar drainage; (3) withdrawal of "unavailable" interstitial fluid within the body by hypertonic solutions given intravenously which act secondarily on the tissue-bound fluid through circulatory, osmotic and metabolic processes; (4) subtraction of the mass or tumor responsible for the disturbance, and (5) subtraction of the brain volume by permitting herniation through an opening in the skull.

Except under conditions of hyperemia, volume A should never be disturbed or subtracted, as the continuation of this volume to its fullest capacity represents survival of the patient. Of all the components, cerebrospinal fluid volume is the least important. Its full subtraction under properly controlled conditions yields the highest volume of circulating blood to the remaining brain tissues and offsets the further loss of brain volume through compression anemia. However, withdrawal of cerebrospinal fluid permits its immediate and active replacement; it is only a temporizing measure.

Any method which first induces the maximum benefits of volume A, the protection of volume B and the continuous withdrawal or reduction of volume C will maintain the highest nutrition and function possible to the cerebral centers. Dehydration, in its ultimate analysis, continues to maintain the cerebrospinal fluid reservoirs at the lowest volume so as to permit the maximum continuation of blood and brain volume.

From a purely mathematical basis, the reasoning and application of the volume relationships may be carried further in an attempt to correlate clinical manifestations with determinations of spinal fluid pressure. When spinal puncture is performed, for every cubic centimeter of cerebrospinal fluid withdrawn an equivalent volume of blood is introduced within the craniovertebral cavity to take its place; whether this is in the perivertebral dural sinuses or in the cerebral capillary circulation is, for the moment, unimportant. No spinal fluid is obtained, even though the system is filled, if some other volume does not enter to take its place, because the walls of the container cannot collapse. Too frequently the operator performs a lumbar puncture without appreciating that the fluid escapes only because an equivalent volume of blood enters the craniovertebral cavity. Thus, "pressure" is in reality an expression of the resistance relationship of the three volume components.

The fact that improvement in cerebral function occurs when proper drainage of spinal fluid is instituted, and that the manifestations of improvement are usually transitory, is due to the fluctuation in available cortical volume. Cerebral function improves with the "high tide" of blood volume, and a "low tide" of spinal fluid volume temporarily exists. If blood volume is allowed to return to the circulation long enough for the spinal fluid reservoir to be refilled, a "high tide" of spinal fluid ensues which hydraulically compels a simultaneous "low tide" of blood volume and a consequent return of undesirable symptoms.

Purgation, bleeding and sweating are direct and indirect methods of attack on all forms of human ills and have gained for themselves throughout the history of medicine sufficient credit to be looked on as generally beneficial. Those of the

medical profession who are concerned with dehydration continue to use these long recognized methods of maintaining a "low tide" of fluid in the body tissue reservoirs for continued periods because of the reciprocal benefits derived in the "high tide" of circulating blood to the brain and the possible resulting increase in function and activity.

That "fluid limitation" will produce "dehydration" is obviously absurd unless the limitation comprises all sources of fluid to the point that the body must withdraw definite amounts from its own reservoirs. It usually will not do this unless the total supply of fluid is inadequate, for its basic reservoirs are well maintained and guarded zealously. To limit the intake of fluid and to permit free ingestion of food or an equal amount of liquid in the diet is a delusion and not worthy of the intelligence of the medical profession which has attempted such a program.

Fluid administered through enemas or other sources immediately destroys the possibility of effecting dehydration, as the body will usually take up fluid from any source available rather than subtract it from its own tissue reservoirs.

In the last analysis, dehydration means the subtraction of water from the patient's body tissue, not from his diet alone. Dehydration may be obtained by strict limitation of fluids in the diet, purgation, intravenous administration of hypertonic solutions, spinal drainage and sweating (even blood letting, if necessary). The method of its production should suit the requirements of the case.

The benefits from dehydration, notably in the epileptic, eclamptic, posttraumatic, spastic and deteriorated states, are not mysterious, nor have they anything to do primarily with the actual program of fluid limitation. The improvements noted are the secondary results of permitting a maximum volume of blood circulation to the cortical tissue, bringing better possibilities for oxygenation and nutrition, metabolism and function. In the end, this means more intelligent and efficacious functioning of the remaining cerebral structures through the proper control and maintenance of the volume "tide" of the cerebrospinal fluid reservoir. "Cures" for such conditions are obviously impossible; improved possibilities for "control" and intrinsic development are the therapeutic objectives.

DISCUSSION

DR. D. J. MCCARTHY: I agree with everything that Dr. Fay said, though I am out of touch entirely with the surgical side of the presentation. From the medical side there are certain facts that have never penetrated my consciousness. It may be agreed that dehydration is good treatment in epilepsy; in our office, when Dr. Fay directed the treatment there were better results than with other types of treatment that we had used for years.

Another question is whether epilepsy is purely a matter of water. If I drank several quarts of water each day I should show no epileptiform symptoms. In epilepsy and in other conditions there must be other factors to cause the convulsions that yield to dehydration. In other fields I find myself in difficulty. I cannot, for example, take an unconscious patient with contracted kidneys and, reversing the training of years, decrease the intake of water; yet I saw Dr. Fay do this with good results. In uremic states, besides the wet-brain there is toxemia. While this is an exceptionally valuable contribution, one must not stop there but must ask what a convulsion is and what epilepsy is. I am not satisfied with any interpretation of epilepsy or of the mechanism of the production of a convulsion, epileptic or otherwise. Dr. Fay, notwithstanding that others may have tried various treatments for epilepsy somewhat similar to his, has made a valuable contribution to the understanding and treatment of this condition.

DR. SAMUEL B. HADDEN: I do not believe that any one can disagree with the basic principle in Dr. Fay's presentation. It is axiomatic that no two bodies can occupy the same place at the same time, and this is the basis of the paper. Dr. Fay's work on the problem of dehydration is a contribution to the control of intracranial pressure. The method, of recent development, is a modification of older methods. Dehydration is one of the oldest methods of treatment for various

diseases. Giving large quantities of salt by mouth is an ancient Chinese treatment for epilepsy. The first epileptic fit that I saw was treated by an old woman who thrust a handful of salt into the mouth of the patient.

Like Dr. McCarthy, I find it difficult to accept all the claims of those advocating dehydration. Dr. Fay presents statistics showing improvement in the results of the management of head injuries. In the past ten or fifteen years there have been many other improvements in technic which are responsible for some of the improved results attributed to dehydration. The automobile, which accounts for the considerable increase in the number of head injuries, also accounts for the arrival of the patients at the hospital much earlier than previously. Today brain injuries rather than fractures of the skull are treated. No longer does one see patients in a state of shock being rushed to the x-ray room for a roentgenogram of the skull. In many other ways the technic in hospitals has improved so much that it must be credited with some of the improvement that is attributed to dehydration.

In the evaluation of dehydration in the management of epilepsy one must realize that the mode of living of many of the patients has been greatly altered by increase in athletic activities and other forms of exercise, which effects some degree of dehydration. As a result of exercise, cerebral circulation is improved and proper oxidation of brain tissue occurs.

I again wish to emphasize the basic correctness in Dr. Fay's presentation, which shows why the various measures of dehydration, bleeding, sweating, purgation and subtemporal decompression will continue to be of value in the management of increased intracranial pressure.

DR. TEMPLE FAY: I appreciate Dr. McCarthy's comments, but wish to emphasize that I did not touch on the etiology of epilepsy or the cause of the convulsion. I merely outlined the results obtained during the past eight years with dehydration as a therapeutic means. Dr. McCarthy mentioned the "10 liter man," and this, of course, clearly illustrates the point at issue. If fluids are properly eliminated, such a capacity produces little cerebral disturbance. However, when the kidneys and skin fail to compensate for the excessive amount of fluid, symptoms similar to those seen in eclampsia are encountered.

Not long ago a man who had attempted to qualify for the "10 liter" championship returned home on a cold morning and immediately had convulsions. Prior to this he had been well, active and normal. He was admitted to the hospital suffering from anuresis; he was in stupor, and the blood pressure was 230 systolic and 156 diastolic. Thorough dehydration was accomplished by direct drainage of the spinal fluid, enemas of magnesium sulphate and the withdrawal of all liquid for twenty-four hours. The convulsions ceased; the blood pressure returned promptly to normal (126 systolic and 84 diastolic), and he was conscious again in a few hours. The renal mechanism gradually regained its former activity, and he was discharged from the hospital, symptom-free, four days later. This is a case with all the symptoms of "eclampsia." The essential hypertension, or "toxemia," if properly diagnosed, would probably have been called alcoholic wet-brain. I do not know what so-called toxemia really is; this is a poor term which covers a great many unknown quantities in medicine. If a therapeutic method is accepted which can preserve the cerebral centers so as to maintain a better control not only of consciousness and the convulsive seizures but of the more vital centers of respiration, blood pressure, pulse and temperature, there may be sufficient time in which to divert or alter the pathologic processes so that the patient may return to a degree of compensation that may be termed recovery.

Dehydration, in the last analysis, only makes possible a better blood volume within the cranial cavity, better oxygenation to the brain centers and, consequently, better function. It does not alter or correct the fundamental pathologic process but merely temporarily prevents the serious secondary effects of cerebral edema and compression.

Dr. Hadden spoke of the early use of the limitation of fluids in the treatment of epilepsy. Hippocrates noted that the "brains of the epileptic were unusually moist," and stated: "He whosoever maketh the body humid or dry, hot or cold

by regimen will cure this disease." The interpretation which the word "cure" has had in recent years is not its original meaning. A certain degree of finality has been accepted in this term; alteration or improvement is probably what was originally meant.

There is no "cure" for diabetes; that is, one cannot replace the islands of Langerhans. One may, however, control the symptoms which this deficiency produces by proper diet and the use of insulin. There is no "cure" for tertiary syphilis of the nervous system, but one may arrest and partially improve the damage which has been done by the disease. The problem of epilepsy should be viewed in a similar light. There is no "cure" for the pathologic destruction and loss of brain tissue. However, better efficiency may be obtained from the remaining nerve elements if proper nutrition can be maintained.

Marcus Aurelius Selcus gained great prominence in Rome for his results secured by causing epileptic persons to fast, which, of course, involved the limitation of fluids in foods. In one of the apocryphal books of the Bible, which dates back to an early manuscript, and in which some of the miracles of Christ are described, there appears this paragraph: "And they brought unto him one who frothed and fell, and He said unto them, I cannot remove the Evil Spirit from him; take him and fast him, and he will recover."

It is probable that the Great Physician and Healer recognized that the epileptic patient between attacks is apparently normal and does not have "the evil spirit" in him. If the predisposing cause for the convulsion was not active at the moment, it could not be removed, but the prescription of fasting which was suggested has been found to bring about recovery in many instances. It seems to me that this paragraph may have been subtracted from the original testimony regarding Christ because it implied his inability to rectify a state which his Divinity should have made possible, and the old judges of this statement accredited to Him might easily have inferred that it was an admission of failure and hence not conceivable of Christ, whereas in reality the statement involves a profound truth, already known to Hippocrates.

As I look back only a few years to the time when conditions related to headache, vomiting, stupor, convulsions and coma were without a logical means of treatment I see the beneficial results which have been obtained in brain tumors, head trauma, posttraumatic symptom complexes of chronic intracranial pressure, hydration states, with low grade hydrocephalus, eclampsia, epilepsy, hypertension and spastic diplegia, and even in cerebral thrombotic manifestations in varying degrees, by the intelligent application of the principles of hydraulics within the cranial cavity.

In the various conditions reported at this meeting a distinct percentage of improvement is seen over the accepted figures of even five years ago. The reduction in mortality from head injuries and eclampsia alone makes the use of dehydration justifiable and of profound importance.

It must be borne clearly in mind that the methods of dehydration, whether by direct withdrawal of spinal fluid (in cases that require this means of correction) or by the secondary effects of limitation of fluid, with purgation, and the intravenous administration of hypertonic solutions, have as a similar objective the diminution of the volume of cerebrospinal fluid, as well as of interstitial fluid within the cranial cavity, and consequently the replacement of this volume by circulating blood, with the beneficial effects which may arise through better oxygenation and nutrition to the failing cerebral centers. If the clinician will adopt an intelligent and comprehensive plan of attack, using the principle of dehydration as a means to this end, he will obtain the results which are possible through the normal mechanism of a better cerebral circulation.

Book Reviews

Forty Years in Psychiatry. By William A. White, A.M., M.D., Sc.D. Nervous and Mental Disease Monograph Series, No. 57. Price, $3. Pp. 154. New York and Washington: Nervous and Mental Disease Publishing Company, 1933.

The last forty years in any field of human endeavor can be said to be unquestionably interesting, but how infinitely more interesting has been the last forty years in psychiatry, a period which has seen practically the development of all present-day psychiatry. Dr. White has been in intimate touch with every nook and corner of the psychiatric field during these forty years and is one of the few present-day psychiatrists who is capable of presenting this narrative. His purpose was not to write an autobiography or to give an exhaustive survey of the scientific psychiatric field all through this period. He has endeavored to give and has succeeded in giving an intensely interesting picture of the movement that has taken place in psychiatry during his experience. Although a story of his experience, it is more a study of the actual detailed progress that has taken place in the life of every progressive psychiatrist and psychiatric group. Based on his experience in St. Elizabeth's Hospital, Washington, a great deal of description and advice are given concerning the state hospital of the future and the part it undoubtedly will continue to play in being the fountain-head of real psychiatric progress.

In the later years with which the book deals White traces the advances that the psychiatric field has made in coming from the custodial care of the old hospital to the gradually improving general medical and psychiatric care of the present state hospital. He carries the movement forward into the days of psychotherapy, mental hygiene and psychoanalysis and shows how the latter movements, bubbling forth at first, have now boiled over into all phases of psychiatry and have influenced through the development of medical psychology the entire field of medicine.

Special chapters that are unusually interesting are: chapter 9, The Value of the Idea—Psychoanalysis; chapter 13, Extra-mural Developments; chapter 14, The Mind Comes into Its Own [meaning replaces description]; chapter 15, Medical Psychology [this chapter touches briefly Dr. White's book "Medical Psychology"; of the same series of publications, which is an interesting production]; chapter 16, Hospital Administration, and chapter 17, The Modern Hospital for Mental Diseases—a chapter that states definitely Dr. White's views regarding the future of the large hospital.

This book, like every book by the same author, is smoothly written, easy to read and most enjoyable and informative. Every medical student who has the slightest interest in psychiatry should read it carefully; from it he cannot help but gain a greater breadth of vision and conception of what psychiatry may mean for him. Any person who has the slightest contact with the psychiatric field, whether through medical associations or otherwise, likewise should read it and discover what bearing psychiatry has on humanity and civilization in general.

Die Blut-Liquorschranke. By F. K. Walter. Price, $5.32. Pp. 223. Leipzig: Georg Thieme, 1929.

This monograph will be of value not only to those interested in the "blood-cerebrospinal fluid barrier" but to all workers in the field of cerebrospinal fluid chemistry, because of the discussion of the nature of the cerebrospinal fluid and the extensive bibliography.

Walter's method for studying the permeability of the blood-cerebrospinal fluid barrier consists in the determination of the relative concentration of bromide in blood serum and cerebrospinal fluid after the administration of sodium bromide by mouth for five days. He found the concentration of bromide in the blood serum

to be about three times that of the bromide in the cerebrospinal fluid, giving a normal permeability quotient of from 2.9 to 3.5. He reports more than four hundred personal observations on the permeability quotient for bromide in various diseases. He found an increased permeability (decreased permeability quotient) in syphilis of the central nervous system, especially in dementia paralytica, and in cerebral arteriosclerosis, while in schizophrenia the permeability is decreased (increased permeability quotient). Walter (and others) attach considerable importance in both differential diagnosis and interpretation of disease processes to changes in the permeability quotient.

Unfortunately, the author gives no criteria for judging the accuracy of the method used for comparing the bromide content of blood serum and cerebrospinal fluid. Because of the possible complexity and variability in composition of gold chloride solution and because of the influence of the concentration of chloride on the color developed in gold chloride by bromide, rigid examination of the accuracy of the method is necessary before his findings may be accepted. Moreover, the acceptance of from 2.9 to 3.5 as the normal range of the permeability quotient is not justified on the basis of the few normal cases studied. It is unfortunate that a method should be widely applied clinically and be the basis for theoretical deductions as to the pathogenesis of disease processes before its reliability has been thoroughly tested.

A Text-Book of Neuropathology. By Arthur Weil. Price, $5. Pp. 335, with 260 engravings. Philadelphia: Lea & Febiger, 1933.

In the preface the author states: "This book has been designated to give a review of the present stage of our knowledge in neuropathology. It contains a collection of facts which have been scattered in the literature and should enable the student to obtain a better understanding of the reaction of the nervous system in disease and to guide him in his clinical work. At the same time, it should help the neurologist to recall data and to point out to him the many problems in the etiology of nervous disease which are still to be solved." On the whole, the book comes up to this promise, but some of it is a rather uninspired stringing together of facts gleaned from the literature and from personal experience. In places the ideas are not clearly expressed, and often the headings of sections are misleading, as when "globoid bodies" within the nerve cells and "vacuole formation" are discussed under the heading "Incrustations" (page 41), and calcium and iron deposits, under the heading "Lipoids."

When the author discusses chemical and physical data he rises above the level of the authors of most such textbooks in that he shows an intimate knowledge of fixation, embedding and staining. He wisely emphasizes the many artefacts that may occur, and points out that formaldehyde is by no means a good universal fixative for nerve tissue. He is also to be complimented on pointing out the important changes that may arise post mortem from the activity of infectious agents and ferments.

The most interestingly presented subjects are inflammation, the mode of invasion, the hemato-encephalic barrier and infections. Encephalitis is discussed from a broad point of view, and the relationships with toxic encephalopathies are indicated. It is rather a surprise to see so-called infectious chorea classified with the degenerative diseases, and one finds it hard to agree with the statement (page 234) that "the idea that Sydenham's chorea is mainly a post-rheumatic manifestation has been abandoned." The many diseases in which demyelinization of the white matter is the prominent lesion are logically collected under the heading "Diffuse Sclerosis." The discussion of the intoxications is less convincing, and that of avitaminosis is scanty. One would also like to see a better discussion of cerebral trauma, now that it is becoming such a common problem; certainly the extensive lesions described ought not all to be gathered under the heading "Concussion." Tumors and congenital malformations are adequately described.

Textbooks are necessary for students and practitioners, and readers and reviewers should deal kindly with the author who puts so much time and effort into correlating facts for them. But why reduplicate effort? There is already a good British textbook of neuropathology. It would seem, moreover, that cooperation among the American neuropathologists might have resulted in one, instead of two, rather similar textbooks of neuropathology within one year (ARCH. NEUROL. & PSYCHIAT. **30**:242 [July] 1933)!

Struktur und Aufbau der biologischen Ganzheiten. By A. Mueller. Price, 9 marks. Pp. 192. Leipzig: Johann Ambrosius Barth, 1932.

Mueller tries to replace the usual objective and purely descriptive view of biologists by the statement of an order of ranks. In the body of the vertebrate, and particularly in the central nervous system, an order of ranks exists in such a manner that the dorsal parts control those on the ventral side, and the cranial parts control those which lie more caudad. The metasyphilitic process prefers those parts of the nervous system which are the highest in rank; this principle is called Kreissotropism (from the Greek word *kreisson*, the superior). This rule manifests itself in metasyphilis by the preference for the regulating elements of the segments (for the posterior roots in tabes) and by the destruction of the functionally highest parts in the cerebellum, in the subcortex and particularly in the cerebral cortex. New facts can hardly be found in this book.

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